

CANADIAN JOURNAL OF RESEARCH

VOLUME 28

NOVEMBER, 1950

NUMBER 11

— SECTION B —

CHEMICAL SCIENCES

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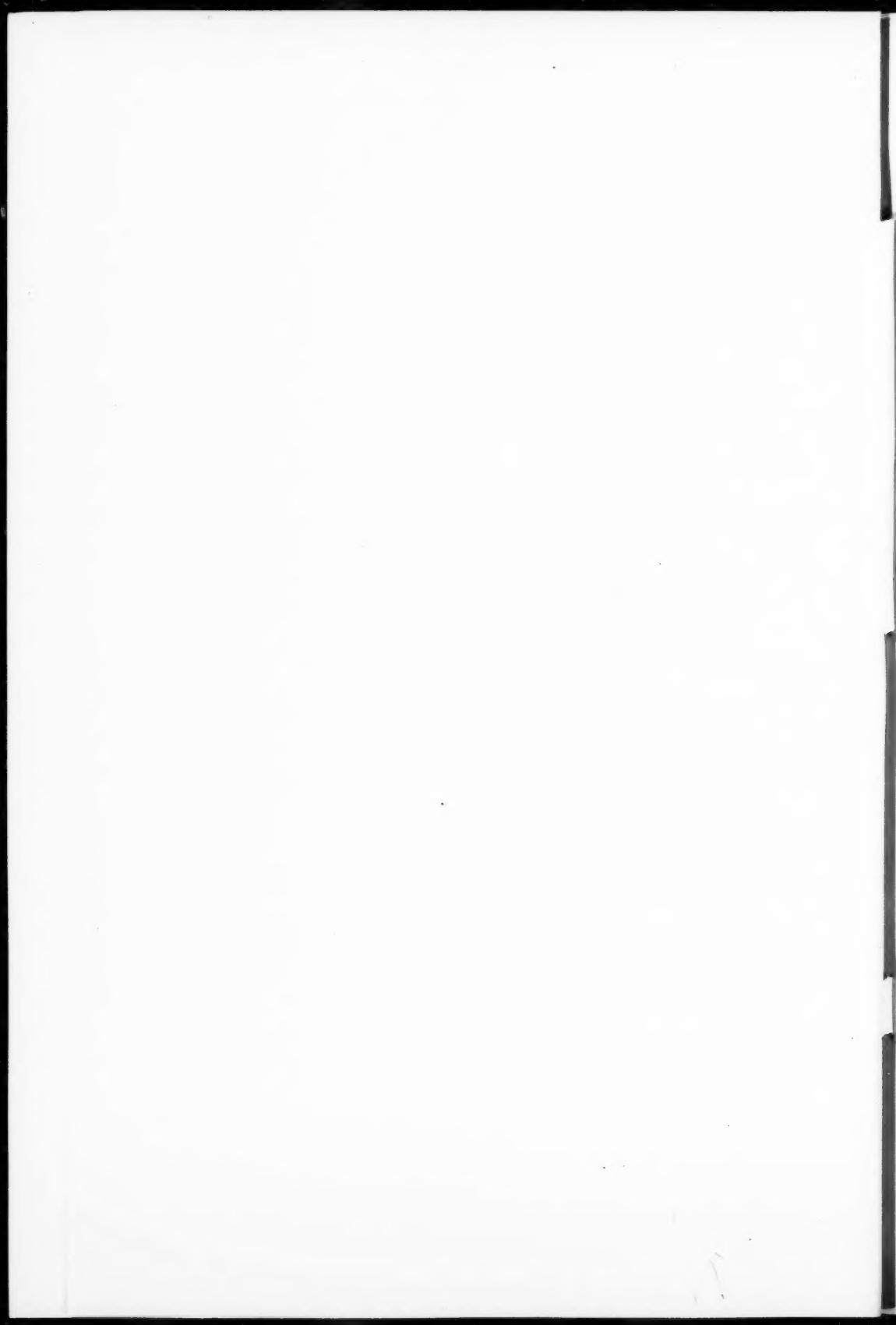
NOTICE

The Canadian Journal of Research is at present published in six sections, A to F. Starting with January 1, 1951, these sections will be published as separate journals under distinctive names and the designation Canadian Journal of Research will no longer be used. The present names and the corresponding new names are as follows:

<i>Present Name</i>	<i>New Name</i>
Canadian Journal of Research, Section A (Physical Sciences)	Canadian Journal of Physics
Canadian Journal of Research, Section B (Chemical Sciences)	Canadian Journal of Chemistry
Canadian Journal of Research, Section C (Botanical Sciences)	Canadian Journal of Botany
Canadian Journal of Research, Section D (Zoological Sciences)	Canadian Journal of Zoology
Canadian Journal of Research, Section E (Medical Sciences)	Canadian Journal of Medical Sciences
Canadian Journal of Research, Section F (Technological Sciences)	Canadian Journal of Technology

In order to preserve continuity the present sequence of volume numbers will be retained, and in each case the volume for 1951 will be Volume 29.

The subscription rates for the Journals will remain as at present.



Canadian Journal of Research

Issued by THE NATIONAL RESEARCH COUNCIL OF CANADA

VOL. 28, SEC. B.

NOVEMBER, 1950

NUMBER 11

THE HYDROLYSIS OF ACETIC ANHYDRIDE IN WATER AND IN THE SYSTEM WATER : METHYL ETHYL KETONE¹

By E. N. BANKS, A. E. MARSHALL, R. W. VOLLETT,
AND R. R. MC LAUGHLIN

Abstract

The rate of hydrolysis of acetic anhydride at 25°C. in water (I), in solutions of methyl ethyl ketone (MEK) in water (II), and in solutions of water in MEK (III) have been studied. In I the observation of previous investigators that the velocity constant varies linearly with the initial concentration of acetic anhydride, but for any given initial concentration of acetic anhydride the reaction is pseudomonomolecular, was confirmed and extended. In II the velocity constant is lower than in I and decreases linearly with increasing concentration of MEK, but, again, the reaction is pseudomonomolecular for any given initial concentration of acetic anhydride. An equation and a nomogram that relate the velocity constant to the initial concentration of acetic anhydride, MEK, and water are presented. In III the second-order rate equation must be modified to compensate for the presumed catalytic effect of the hydrogen ion produced by hydrolysis.

Introduction

The hydrolysis of acetic anhydride in water has been the subject of many previous investigations, notably those of Rivett and Sidgwick (4) and Orton and Jones (3). Orton and Jones recalculated the results of Rivett and Sidgwick to conform with their own and confirmed the fact that the velocity constant varies with the initial concentration of the acetic anhydride. The first part of this paper verifies and extends their results. Orton and Jones (3) also reported the effect of addition of acetone to the aqueous reaction medium, stating, for example, that in 50% water-acetone system the rate of hydrolysis of the anhydride is only about one-third of the rate in aqueous acetic acid of like anhydride concentration. This is the only reference found in the literature concerning the effect of ketones on this hydrolysis. In sections two and three of the present paper the rates of hydrolysis of acetic anhydride in aqueous solutions containing methyl ethyl ketone (MEK) and solutions of MEK containing water are reported and discussed.

Since it is difficult to measure the exact moment when hydrolysis of acetic anhydride in dilute solutions begins, the first-order equation was integrated between the limits t' and t'' , yielding the expression

$$K = \frac{2.303}{t'' - t'} \log \frac{A_0 - x'}{A_0 - x''}$$

(where A_0 is the initial concentration, and x is the amount which has reacted after time t) which was used in making the calculations in Sections 1 and 2.

¹ Manuscript received in original form April 13, 1950, and, as revised, August 30, 1950.
Contribution from the Department of Chemical Engineering, University of Toronto,
Toronto, Canada; from a thesis presented by three of the authors (E.N.B., A.E.M., R.W.V.) for
the degree of B.A.Sc.

In Section 3 the concentrations of acetic anhydride and of water were approximately the same. Since the integrated form of the equation for reactions of the second order did not give constant values of K , the equation

$$-\frac{dx}{dt} = K(A_0 - x)(B - x),$$

where B is the initial concentration of the second reacting substance, was modified before integration. In the modified form the equation gave constant values of K .

Experimental

Section 1: The Hydrolysis of Acetic Anhydride in Water at 25°C.

In the initial stages of the investigation the work was performed to check the experimental method, and to confirm the results reported by Rivett and Sidgwick (4) and Orton and Jones (3).

A 250 ml. glass-stoppered conical flask containing 125 ml. of distilled water was placed in a thermostat at 25.0°C. A measured quantity of acetic anhydride was added to the flask, which was then stoppered and vigorously shaken. The time was recorded to the nearest second when shaking commenced.

A 10 ml. sample was withdrawn as soon as possible and placed in a 250 ml. bell-mouthed, glass-stoppered flask previously prepared by adding to it 2 ml. of aniline and a few drops of phenolphthalein solution. The flask was then stoppered and shaken, the time shaking commenced being recorded to the nearest second. About 20 ml. of distilled water was then admitted through the bell mouth of the flask and the contents of the flask titrated with standardized sodium hydroxide solution. Samples were taken at about five minute intervals. This analytical procedure is essentially that used by Lumière and Barbier (2).

The portion of the acetic anhydride that was hydrolyzed furnishes two equivalents of acetic acid, while the residual anhydride reacts quantitatively with the aniline to form acetanilide and one equivalent of acetic acid. The amount of acetic acid titrated is, therefore, a measure of the extent to which hydrolysis had proceeded. The titer when hydrolysis is complete less the titer at any time t is proportional to the concentration of the anhydride at the time t .

The value of the velocity constant K was calculated for each run, using the first-order rate equation. The values of K for those runs at the same initial concentration of acetic anhydride were then averaged. In no case was the result of a run accepted unless it checked with the results of other runs within the limit of experimental error, which was about 4%.

The results obtained by Rivett and Sidgwick (4) and recalculated by Orton and Jones (3) appear in Curve 1, Fig. 1, as K versus initial concentration of acetic anhydride. Our first experiment was made with an initial concentration of anhydride 0.785 mole per liter. The average K for six runs was 0.127

reciprocal minute. When this result is placed on the graph it falls on the extrapolated line of Rivett and Sidgwick.

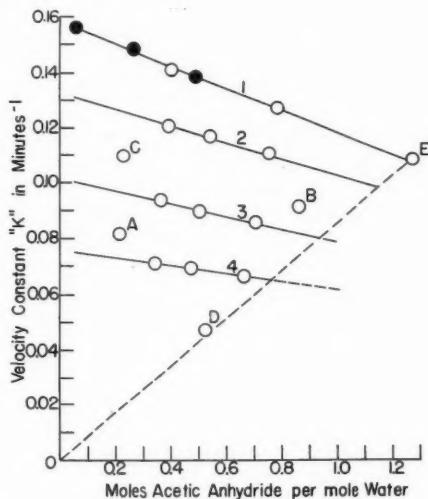


FIG. 1. Dependence of "K" on composition of initial reaction mixture.

Curve	ml. MEK per liter of water
1	0
2	40
3	120
4	200

● Rivett & Sidgwick ○ This paper

As a check, Experiment 2 carried out at an initial concentration of 0.407 mole per liter gave a value of K of 0.141 reciprocal minute, which also falls on the line.

Experiment 14 (E, Fig. 1) was performed with an initial concentration of acetic anhydride of 1.27 moles per liter, which is the limit of solubility of the anhydride in water, and yielded a value of K of 0.109 reciprocal minute. This value is useful since it indicates the limit to which the line can be safely extrapolated.

The equation of this line, which represents the variation of the velocity constant with initial concentration of acetic anhydride, was found to be

$$K = -0.040 A_0 + 0.158,$$

where A_0 is the initial concentration of the acetic anhydride in moles per liter and K is in reciprocal minutes.

If the rate equation is modified to take into account the variation of the velocity constant with the initial concentration of acetic anhydride it becomes

$$\frac{dA}{dt} = -(K' - a A_0)A,$$

where K' and a are constants, A_0 is the initial concentration of acetic anhydride and A is the concentration of acetic anhydride at time t . This leads on integration to

$$t = \frac{2}{K' - a A_0} \ln \frac{A_0}{A}.$$

From experimental results K' equals 0.316 and a equals 0.080. The equations should not be used for values of A_0 less than 0.05 or greater than 1.25 moles per liter. In the former case, as stated by Orton and Jones (3), the relationship is not linear, and, in fact, in more dilute solutions, as reported by Gold (1), there is no anomaly. In the latter case the two-phase region is reached.

Section 2: The Hydrolysis of Acetic Anhydride in Aqueous Solutions Containing Methyl Ethyl Ketone at 25°C.

Seidell (5) gives the solubility of MEK in water at 25°C. as 22.6 gm. per 100 gm. of saturated solution. The second section of the work deals with those solutions in which this ratio of ketone to water was not exceeded. The original samples were prepared by adding a known volume of MEK to 125 ml. of water. The procedure then followed that of Section 1.

Thirteen experiments were performed. As before, at least two runs were made for each experiment and the values of K calculated for each run were averaged to obtain the experimental values plotted in Fig. 1.

The curves in Fig. 1 show that the velocity constant decreases as the initial concentration of acetic anhydride is increased, and as the concentration of MEK is increased.

For any ratio of MEK to water the velocity constant is a linear function of the initial concentration of the acetic anhydride. The equations of these straight lines were derived. The values of the Y -intercept and of the slope of the line were then plotted as ordinates against the number of milliliters of MEK per liter of water as abscissas. These plots again gave two straight lines which showed that the slopes and the Y -intercepts of the lines of Fig. 1 are linear functions of the ratio of MEK to water. Equations were then derived for the variation of the slope and Y -intercept, which, when substituted in the original equation showing the variation of K with concentration of the acetic anhydride, yielded the following equation:

$$K = (1.065 \times 10^{-4}R - 0.0343)A_0 - 3.5 \times 10^{-4}R + 0.145,$$

where A_0 is the initial concentration of the acetic anhydride in moles per liter and R is the number of milliliters of MEK per liter of water. The units of K are reciprocal minutes, and the equation is dimensionally consistent.

A nomogram (Fig. 2) was also prepared using the same data as those used in preparing Fig. 1. Both the nomogram and the equation give values of K which are within 4% of the experimental values. Experiments 17, 18, and 19 (A , B , and C , Fig. 1) were made in order to check the validity of the nomogram after it had been prepared, and the results are shown in Table I.

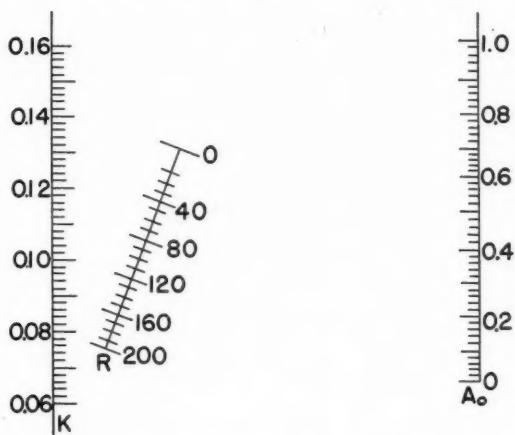


FIG. 2. Nomogram relating the velocity constant K to R , the MEK concentration, and to A_0 , the initial concentration of the anhydride.

TABLE I

Expt. No.	Run No.	A_0 = moles Ac_2O per liter	R = ml. MEK per liter H_2O	K	Av. K	Calc'd. K	K nomo.
17	1	0.215	160	0.0826	0.0813	0.0853	0.0840
	2	0.215	160	0.0800			
18	1	0.863	80	0.0919	0.0912	0.0947	0.0935
	2	0.863	80	0.0905			
	3	0.863	80	0.0913			
19	1	0.230	80	0.1134	0.1138	0.1148	0.1100
	2	0.230	80	0.1141			

The equation and the nomogram should not be used for concentrations of the anhydride less than 0.05 or greater than 1.25 moles per liter for the same reasons as in Section 1. Further, for ratios of MEK to water less than 25 ml. per liter the equation will yield low values of K , since the initial additions of MEK are proportionately more effective in lowering the value of K than subsequent additions.

Experiment 6 (*D*, Fig. 1), using 280 ml. of MEK per liter of water and a concentration of anhydride of 0.525 mole per liter, showed the presence of a small amount of a second phase. The velocity constant for this experiment was 0.047 reciprocal minute. A line joining the origin and the points representing the results of Experiments 6 (*D*, Fig. 1) and 14 (*E*, Fig. 1) represented the lower limit of the graph, below which two phase systems would be met.

In general the hydrolysis of acetic anhydride in aqueous solutions containing small amounts of MEK is pseudomonomolecular. The velocity constant is

decreased by increasing the initial concentration of the acetic anhydride and by increasing the ratio of MEK to water. For these solutions the hydrolysis of the acetic anhydride may be regarded as complete in two hours.

Section 3: The Hydrolysis of Acetic Anhydride in Methyl Ethyl Ketone Containing Water at 25°C.

The amount of water used did not exceed its solubility in MEK at 25°C. (9.9 gm. per 100 gm. solution).

The experimental method followed generally that of Sections 1 and 2.

During the initial stages of the hydrolysis a number of facts became evident. The initial titer was considerably higher than expected. Subsequent volume measurements indicated that there was an appreciable volume change on mixing, and further, that the volume altered as hydrolysis proceeded.

The initial concentrations of water and anhydride used were such that a second-order reaction rate would be expected. However, when the titration values were plotted against time the rate of hydrolysis at first increased abnormally (See Fig. 3) and later decreased, in the normal manner.

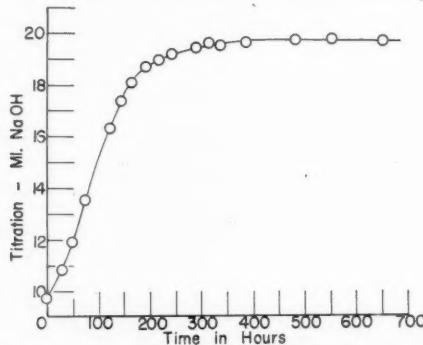


FIG. 3. Rate of hydrolysis at 25.0°C. of acetic anhydride in methyl ethyl ketone. Solution contains 0.490 mole acetic anhydride (A_0) and 2.481 moles water (B) per liter.

The pH of a sample was measured after hydrolysis was complete and found to be 3.75. From this fact and the initial concentration of the acetic anhydride (0.490 mole per liter) the dissociation constant for acetic acid in methyl ethyl ketone was calculated to be 3.27×10^{-8} .

It is known that hydrogen ion sometimes catalyzes hydrolysis. It was assumed that this effect would be linear with the hydrogen ion concentration and that the velocity constant would therefore be proportional to the square root of the acetic anhydride that had been hydrolyzed at any time. In the differential form the rate equation would become

$$\frac{dx}{dt} = K(A_0 - x)(B - x)x^{\frac{1}{2}},$$

where B is the initial concentration of the water. On integration this gives

$$Kt = \frac{1}{(B - A_0)A_0^{\frac{1}{2}}} \ln \frac{A_0}{A_0 - x} + \frac{1}{(A_0 - B)B^{\frac{1}{2}}} \ln \frac{B}{B - x} + \frac{2x^{\frac{1}{2}}}{A_0 B}.$$

Since the second-order rate equation did not give constant values of K , the above equation was used in all calculations for this section.

Three experiments were performed using an MEK to water ratio of 20 to 1 by volume. Because of volume changes the final titration differs from that calculated from the initial concentrations. Corrections to titrations performed during the run were made on a linear basis.

Table II gives the results obtained for the three experiments.

TABLE II

Expt. No.	Initial conc. of anhydride, moles per liter	Initial conc. of water, moles per liter	K
13	0.490	2.481	0.0133
15	0.938	2.404	0.0139
20	0.731	2.405	0.0134
			Av. 0.0136

Time measurements were made in hours. The units of the terms in the equation are consistent and equal to time⁻¹ × concentration^{2/3}.

A further experiment was done in which the concentrations of acetic anhydride and water were both 2.38 moles per liter and the ratio of MEK to water was 17.5 to 1 by volume. For equimolar concentrations the integrated form of the equation is

$$Kt = \frac{1}{A_0^{\frac{1}{2}}(A_0 - x)} + \frac{2}{A_0^{\frac{3}{2}}} x^{\frac{1}{2}} - \frac{2}{A_0^{\frac{3}{2}}}.$$

There was some fluctuation of the final titration value even after 900 hr. The value of K , however, averaged 0.0087. This would indicate that the value of K is again a function of the ratio of MEK to water.

The hydrolysis of acetic anhydride in MEK is extremely slow. Hydrolysis is about 90% complete after 10 days. The reaction does not follow the simple second-order equation and appears to be complicated by the catalytic effect of the hydrogen ion produced during hydrolysis.

Acknowledgment

The authors wish to acknowledge the assistance received from Professors W. C. Macdonald and G. W. Minard.

This problem was suggested by Shawinigan Chemicals Limited, and information received from them is gratefully acknowledged.

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1. GOLD, V. Trans. Faraday Soc. 44: 506. 1948.
2. LUMIÈRE, A., LUMIÈRE, L., and BARBIER, H. Bull. soc. chim. France, 35: 625. 1906.
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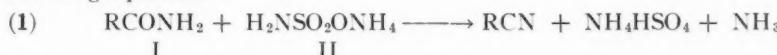
SYNTHESIS OF NITRILES BY FUSION OF AMIDES WITH AMMONIUM SULPHAMATE¹

BY JEAN L. BOIVIN

Abstract

It has been found that a good yield of nitriles can be obtained by fusing amides with ammonium sulphamate. The method has been applied successfully to simple aliphatic and aromatic amides. There is evidence that the mechanism of this transformation involves reaction between amides and ammonium sulphamate, giving rise to ammonium N-alkoyl or N-arylsulphamates which rearrange into ammonium bisulphate and nitriles.

During the course of a study carried out in this laboratory on nitriles, it was found that these substances could be prepared by the fusion of amides (I) with either ammonium sulphamate (II) or a mixture of sulphamic acid and ammonium carbonate at 180–210°C. The reaction takes place with the liberation of ammonia and the formation of ammonium bisulphate according to the following equation:—



The above reaction was carried out, using various amides as starting materials. Liquid nitriles were distilled over, whereas solid nitriles were extracted with a suitable solvent.

The ease of this preparation and the good yields obtained (see Table I) compare favorably with the usual methods of preparing nitriles. The main disadvantage lies in the high cost of the ammonium sulphamate. This was minimized, however, by preparing it *in situ* by heating equivalent amounts of ammonium carbonate and sulphamic acid which is now manufactured from urea and fuming sulphuric acid (4, 7). The yields reported in Table I were obtained by fusing equimolar quantities of reagents. However, nearly quantitative yields were obtained on employing a small excess of ammonium sulphamate.

The transformation of amides into nitriles is known to take place through dehydration of the amide (6). It was of interest to know what role ammonium sulphamate played in this dehydration.

Since according to Equation (1) one mole of ammonium bisulphate is formed from one mole of ammonium sulphamate, it could be thought that the essential dehydration step comprises the reaction:—

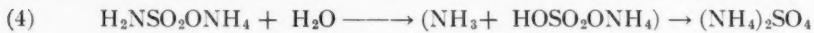


At high temperatures the escape of ammonia would be promoted, thus preventing further reaction to ammonium sulphate according to the following equation:—



¹ Manuscript received June 9, 1950.
Contribution from the Organic Section of the Canadian Armament Research and Development Establishment, Valcartier, P.Q.

On this basis, it would be expected that in aqueous solution, ammonium sulphamate would readily add water in accordance with the following scheme:-



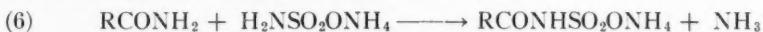
Actually, such addition of water to ammonium sulphamate does not take place at all readily. After refluxing for 15 hr. in aqueous solution, ammonium sulphamate was recovered almost intact and only traces of sulphate could be detected. Again, whereas glycerol yields acrolein when heated in the presence of a dehydrating agent, the fusion of ammonium sulphamate with glycerol at 200°C. gave no acrolein and only traces of sulphate.

From the above data, it is evident that ammonium sulphamate does not behave simply as a normal dehydrating agent, and an alternative reaction mechanism must be sought.

Berglund (2) reported that the fusion of sulphamic acid alone yields sulphur dioxide, sulphuric acid, nitrogen, and water. He also stated that ammonium sulphamate (m.p. 131°C.) when heated at about 170–180°C. is transformed into ammonium imidodisulphonate (III) and ammonia (Equation (5)).



By analogy it appeared possible that a mechanism involving an initial condensation with elimination of ammonia, followed by internal rearrangement and splitting, would account for nitrile formation.



In order to prove this mechanism of formation of nitriles by the action of sulphamates on amides, the following experiments were made. Firstly, the stoichiometric quantities illustrated in Equation (1) were verified by analysis. When equimolar amounts of acetamide and ammonium sulphamate were fused, nearly one mole of ammonia was evolved while acetonitrile was isolated in 90% yield.

The total sulphate present in the residue was found to be equal to 1.01 moles. However, the ammonia formation in this reaction (Equation (6)) is not entirely conclusive, since the sulphamate fused alone gives half a mole of ammonia (Equation (5)).

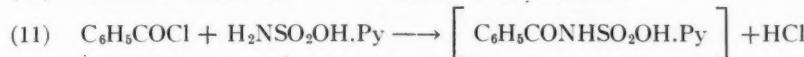
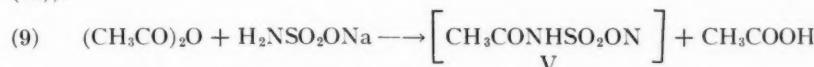
Ammonium N-benzoylsulphamate (IV, R: C₆H₅) was synthesized unequivalently by reacting benzamide with a solution of sulphuric acid in acetic anhydride. The benzamide salt of N-benzoylsulphamic acid was converted by means of ammonia into compound IV. This salt, which is not described in the literature, had a melting point of 190–191°C. A cold aqueous solution of this N-substituted sulphamate showed no precipitation with barium ion, but, at the boiling point, barium sulphate was formed. Moreover, cold dilute nitric

acid oxidized IV to a sulphate; it is known from the work of Baumgarten (1) that sulphamic acid or its salts could be oxidized to sulphuric acid.



When ammonium N-benzoylsulphamate was heated above its melting point, benzonitrile and ammonium bisulphate were isolated in quantitative yield, no ammonia being produced during the fusion (Equation (7)).

The same reactions were carried out, although not as clearly, owing to difficulties of purification of intermediate products, when sodium sulphamate was treated with acetic anhydride to give rise to the expected sodium N-acetyl-sulphamate (V). The residue, after evaporating the reaction mixture to dryness, was heated in the usual way, whereupon acetonitrile distilled over and sulphates were formed (Equations (9) and (10)). Similarly, the action of benzoyl chloride on sulphamic acid in a pyridine solution gave a product from which benzonitrile was obtained on heating the residue (Equations (11) and (12)).



From this study it is concluded that the transformation of amides into nitriles by means of ammonium sulphamate is not a simple dehydration. It involves deamination and condensation between the amides and ammonium sulphamate, giving rise to ammonium N-alkoyl or N-aroylsulphamates which rearrange into nitriles.

Experimental

Preparation of Nitriles

(a) *Liquid Nitriles*

In a distilling flask equipped with a short column were placed finely powdered sulphamic acid (9.7 gm., 0.10 mole), ammonium carbonate (9.6 gm., 0.05 mole), and an amide (0.10 mole). The mixture was heated in a metal bath at 100–120°C. whereupon the formation of ammonium sulphamate took place with evolution of carbon dioxide. Then the temperature was raised to 150–160°C. whereupon ammonia was evolved and the ammonium N-alkoyl or N-aroylsulphamate was formed. At 190–200°C., the nitrile was produced and distilled over. The results are shown in Table I.

(b) *Solid Nitriles*

The proportions used were the same as in the above preparation and the heating was effected in the same way. When reaction was complete, the mix-

ture was cooled and boiled with water to dissolve the ammonium salt. The water insoluble material was filtered, washed with water, and crystallized from a suitable solvent. The results are summarized in Table I.

TABLE I
PREPARATION OF NITRILES, RCN

R	B.p., °C.	M.p., °C.*	n_D^{20}	% Yield†
CH ₃	81–82	—	1.3460 ²⁰	90
C ₂ H ₅	96–97	—	1.3689 ¹⁵	91
C ₃ H ₇	117–118	—	1.3816 ²⁵	90
C ₆ H ₅	190–191	—	1.5200 ²⁰	85
p-NO ₂ -C ₆ H ₅	—	146–147	—	92

* All melting points are uncorrected.

† Yields obtained from equimolar amounts of amides and ammonium sulphamate.

An excess of 0.2 mole of ammonium sulphamate gave a nearly quantitative yield.

Ammonia and Sulphates Formed in the Reaction

In a distilling flask, a mixture of ammonium sulphamate, m.p. 131°C. (11.4 gm., 0.10 mole) and acetamide (5.9 gm., 0.10 mole) was fused in the manner described above. The ammonia eliminated during the reaction was swept from the flask by a stream of nitrogen and absorbed in an acid solution. The amount of ammonia titrated was equal to 1.62 gm., which is equivalent to 0.095 mole. The residue, after the acetonitrile had been distilled over, was analyzed as it was. Calc. for SO₄HNH₄: SO₄, 83.5%; NH₃, 14.8%. Found: SO₄, 84.3%; NH₃, 15.1%. Since nitric acid readily oxidized sulphamic acid, the precipitation of barium sulphate was made in dilute hydrochloric acid.

Heating of Ammonium Sulphamate with Water and Glycerol

Ammonium sulphamate, fused alone at 180°C. and then at 300°C., gave a good yield of ammonium imidodisulphonate (5). When ammonium sulphamate was boiled under reflux for 15 hr., no ammonia was evolved and the starting material was recovered unchanged. A mixture of ammonium sulphamate and glycerol heated at 200–220°C. did not yield acrolein.

Ammonium N-Benzoylsulphamate (IV, R: C₆H₅)

To a cold mixture of acetic anhydride (70 gm.) and concentrated sulphuric acid (9.6 gm., 0.098 mole) was added benzamide (24.2 gm., 0.2 mole). The mixture was stirred at room temperature. When all the benzamide was dissolved, a new crystalline solid separated out. The mixture was allowed to stand in the refrigerator overnight. The solid was filtered, washed with acetic anhydride, and finally several times with anhydrous ether. This benzamide salt of N-benzoylsulphamic acid melted at 150–151°C., instead of 145–146°C. as reported by Büchner (3). Yield, 30.5 gm. (94%). This sulphate-free substance was dissolved in cold ammonium hydroxide (10%, 200 ml.). Benzamide, which

separated out, was filtered, while the aqueous layer was extracted several times with ether to remove any dissolved benzamide. Then the aqueous solution which was free from sulphate was evaporated *in vacuo*. If evaporation was done at 50–60°C., some sulphate was formed. The crystalline compound obtained melted at 190–191°C. with decomposition. Yield, 20.3 gm. (93% from benzamide). Calc. for C₇H₁₀O₄N₂S: S, 14.6%. Found: S, 14.7%. The sulphur content was determined by boiling the sample in a dilute solution of nitric acid and adding barium chloride.

Benzonitrile from Ammonium N-Benzoylsulphamate

Ammonium N-benzoylsulphamate (2.18 gm., 0.01 mole) was fused at 200°C. for one hour. No ammonia was formed. Benzonitrile distilled over, b.p. 190–191°C. Yield, 0.8 gm. By washing the apparatus and extracting the residue with ether, an additional quantity of benzonitrile was obtained amounting to 0.2 gm. The total yield amounted to 1.0 gm. (97%). By treating the residue with barium ion in dilute hydrochloric acid, 2.35 gm. (0.0101 mole) of barium sulphate was formed.

Action of Acetic Anhydride on Sulphamates

A mixture of acetic anhydride (50 ml.), sulphamic acid (9.7 gm., 0.1 mole), and sodium carbonate (5.3 gm., 0.05 mole) was refluxed for five hours. The mixture was evaporated to dryness under reduced pressure. The residue was heated at 200–220°C. whereupon acetonitrile distilled over, b.p. 82°C., without any formation of ammonia. Yield, 3.0 gm. (73%). The residue, which contained a large amount of sulphates, was not analyzed.

Action of Benzoyl Chloride on Sulphamate

A mixture of benzoyl chloride (14.0 gm., 0.10 mole) and finely divided sulphamic acid (9.7 gm., 0.10 mole) in pyridine (50 ml.) was refluxed for five hours. After the mixture was evaporated to dryness, the residue was heated at 200–220°C., whereupon benzonitrile distilled over, b.p. 190–191°C. Yield, 8.2 gm. (80%). No ammonia was evolved during the distillation. The residue contained a large amount of sulphates.

Acknowledgment

The author wishes to thank Dr. A. L. Lovecy and Mr. Percy Fainer of this Establishment for valuable discussions on this subject, and also the Defence Research Board of Canada for permission to publish this paper.

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A MICROMETHOD FOR THE DETERMINATION OF SUGARS¹

BY J. E. STONE AND M. J. BLUNDELL

Abstract

Certain pentoses and hexoses were determined by measuring spectrophotometrically the yields of furfural and hydroxymethylfurfural obtained on steam distilling with syrupy phosphoric acid. The yields, based on the theoretical recovery, were increased by increasing the temperature and the rate of steam distillation, and by decreasing the amount of sugar. At a steam rate producing 10 ml. per min. of distillate, at 195°C. externally applied temperature, and with 2 mgm. sugar, the yields of aldehyde were from xylose 91.0%, ribose 74.9%, arabinose 60.6%, rhamnose 55.9%, galactose 20.0%, and glucose 15.5%. As little as 0.1 mgm. of each could be determined in this way, the mean deviation being usually less than $\pm 3\%$ and the time required less than 10 min. Mixtures of sugars have been separated on a paper strip chromatogram and the individuals determined, without separate extraction, by steam distilling into phosphoric acid.

Introduction

The separation of a mixture of sugars by paper chromatography has been developed into a quantitative method by extracting the material with water and determining the small amounts of sugars by microtechniques. Thus Flood, Hirst, and Jones (3) used Somogyi's micro copper reagent on the aqueous extract while Hawthorne (4) measured the excess of reagent remaining after oxidation of the sugar with hypoiodous acid. By these methods it has been claimed that the individual components of a sugar mixture can be determined with an error of $\pm 5\%$. The amount of material that can be handled on a conventional paper chromatogram is a few milligrams at most, and it was felt that the very sensitive method of spectrophotometry could be used to advantage if a suitable means were available for converting the sugar into the corresponding furfural derivative. The recent work of Dunstan and Gillam (2) has shown that steam distilling a pure sugar with 85% phosphoric acid gives moderately reproducible results with 0.5–2.0 mgm. of material, and the aqueous distillate obtained with this acid makes it suitable for direct estimation of the furfural by light absorption in the ultraviolet region. However, it was felt desirable to amplify their work before applying it to paper chromatography since the effect of temperature, time, and amount of sugar on the yield of furfural had not been given, and also because the yields stated for the various sugars were not based upon standard furfural curves but upon the assumption that Krober's (6) yield of 88% for xylose was correct. This assumption might not be justified in view of the different acid, amount of sugar, and distilling conditions used by Dunstan and Gillam. The present work was undertaken in order to establish the optimum distilling conditions and to obtain the percentages conversion of single sugars into furfural by comparing the optical density of the distillate with standard furfural curves. A further object was to apply the results so obtained to the analysis of mixtures of sugars via the paper chromatogram.

¹ Manuscript received July 18, 1950.

Contribution from the National Research Council of Canada, Prairie Regional Laboratory, Saskatoon, Saskatchewan. Issued as paper No. 92 on the Industrial Utilization of Wastes and Surpluses and as N.R.C. No. 2231.

Experimental

Materials

The sugars used, xylose, ribose, arabinose, rhamnose, galactose, and glucose, were recrystallized commercial samples. Furfural was the commercial material doubly distilled under reduced pressure to give a colorless product, while the methyl furfural and 5-hydroxymethylfurfural were prepared according to the procedures of Rinkes (9) and Middendorp (7) respectively. All solutions were made using water that had been redistilled from potassium permanganate.

Apparatus

The apparatus is shown to scale in Fig. 1, the chief feature of interest being the chamber marked *A* at the top of the steam inlet tube. The purpose of this chamber is to hold the rolled up strip of filter paper cut from the chromatogram. In this way the separate operations of extracting the sugar and measuring its concentration in the resultant solution is dispensed with, since sufficient condensation occurs in the steam line to wash out the sugar and carry it down into the acid. Any form of control based on the phosphoric acid temperature was impossible, since by the time it had reached a steady value the distillation was practically complete. Hence an oil bath was used which could be lowered and swung out of the way when the reaction tube was being put on, and this provided a constant external temperature. The temperature gradient between the acid and oil varied with the rate of flow of steam but was about 20°–30°C. under equilibrium conditions.

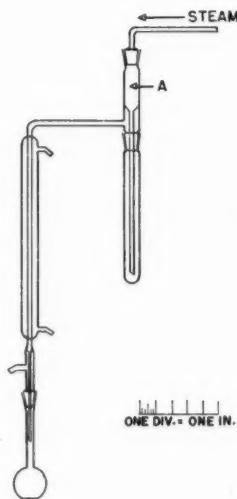


FIG. 1. *Apparatus.*

The Determination of Individual Sugars

The sugars were used in the form of 1% aqueous solutions. The appropriate amount was measured from a microburette into a glass capsule, which was then dropped into the reaction tube containing 5 ml. of 85% phosphoric acid. With the oil bath up to temperature and the steam being generated at the required rate, the reaction tube was placed in position and the distillate, which immediately began to form, collected in a volumetric flask. The intensity of absorption in the ultra-violet at the appropriate wave length was then measured directly or on an aliquot suitably diluted. A Beckman DU Spectrophotometer was used, the wave length of maximum absorption being 276 m μ ., 292 m μ ., and 283 m μ . for furfural, 5-methylfurfural, and 5-hydroxymethylfurfural respectively. Fig. 2 gives the variation in absorption density ($\log \frac{I_0}{I}$) with concentration and the relation is seen to be sensibly linear. It was noted that the furfural solutions deteriorated rapidly on standing, and consequently all measurements on them were made immediately after preparation.

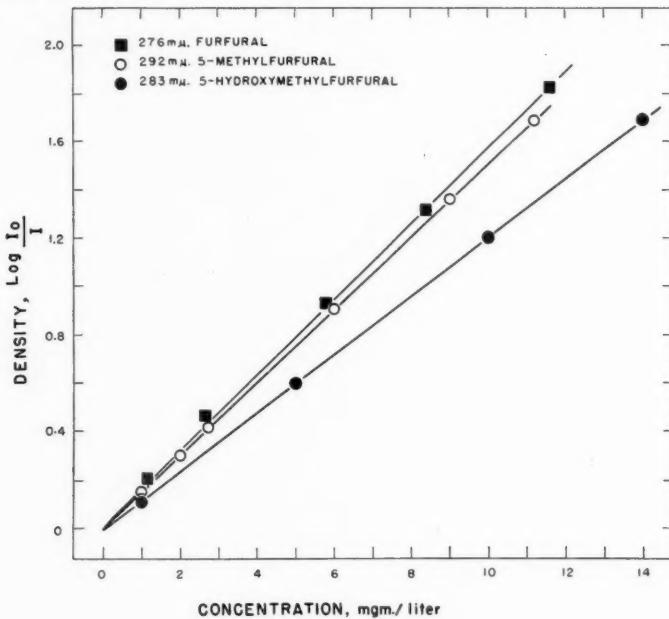


FIG. 2.

The Determination of Sugar Mixtures

The procedure for chromatographic separation followed closely the description given by Flood, Hirst, and Jones (3). A strip of Whatman No. 1 filter paper, 6 in. by 22 in., was used as supporting medium. A pencil line was drawn across it 5 in. from one end and another drawn down the length of the paper

1 in. from one edge. A portion (0.05 ml.) of the sugar mixture, representing 0.5 mgm. of each component (solution 1% with respect to each) was measured from a microburette and spotted or streaked across the base line. A single spot of 0.01 ml. was placed in the inch-wide lane to act as position indicator and the strip then developed by the downward flow method of Consden, Gordon, and Martin (1). Butanol-water or ethyl acetate - acetic acid - water (5) were found suitable solvents, and, after development and drying, the position indicator strip was cut off and sprayed with aniline-phthalate reagent (8). The red or green spot then enabled a strip 2 1/2 in. wide to be cut from the main chromatogram which contained all of that particular sugar, and this strip was carefully rolled and slipped into a ring of platinum wire. The roll, 2 1/2 in. long, was placed in the chamber marked *A* in Fig. 1, the apparatus assembled with 5 ml. 85% phosphoric acid in the reaction tube, and 2 ml. water added to soak the paper. Adding water to the paper was not absolutely necessary but helped the condensation of steam and reduced the volume of distillate required to contain all the furfural. The subsequent procedure was the same as for individual sugars. One hundred milliliters of distillate was usually sufficient, but as a precaution a further 50 ml. was always collected.

Results and Discussion

Single Sugars

The variables which it was considered would have the greatest effect on the yield of furfural were the temperature of phosphoric acid, rate of distillation, amount of sugar, and type of sugar, and they were studied in that order. The first two, temperature and rate of distillation, were studied using xylose, the assumption being made that the other sugars would react similarly to the same changes in conditions. Fig. 3 shows clearly that an increase in temperature from 127°C. to 195°C. reduces the volume of distillate required very considerably and at the same time gives a somewhat greater yield of furfural. Although high yields of furfural have no particular merit, reproducibility being more important, the smaller volume of distillate required is a distinct advantage in an analytical procedure. For all future work, therefore, the oil bath was maintained at 195°C. Varying the steam flow between the limits 2 ml. and 10 ml. of distillate per min. did not alter the results significantly if the same volume were collected. It was maintained at the higher figure in order to reduce the time factor. It may be noted at this stage that the volume of distillate that must be collected increases somewhat with larger amounts of sugar; these volumes, in round figures, are given in Table I. The yields vary from sugar to sugar, downward in the order of the table, and also with the amount of sugar taken for each determination. The second point is in contrast to the findings of Dunstan and Gillam, who claimed that the yields obtained from 0.5 to 2.0 mgm. of these sugars did not vary. While this is so for the hexoses it is certainly not true for the pentoses under the conditions used in this work. Also, unlike those of the above authors, the results for glucose and galactose appeared to be as reproducible as for the other sugars. The mean deviation recorded in Table I seldom exceeds $\pm 2\%$ or the maximum deviation 3%. At 10 ml. per

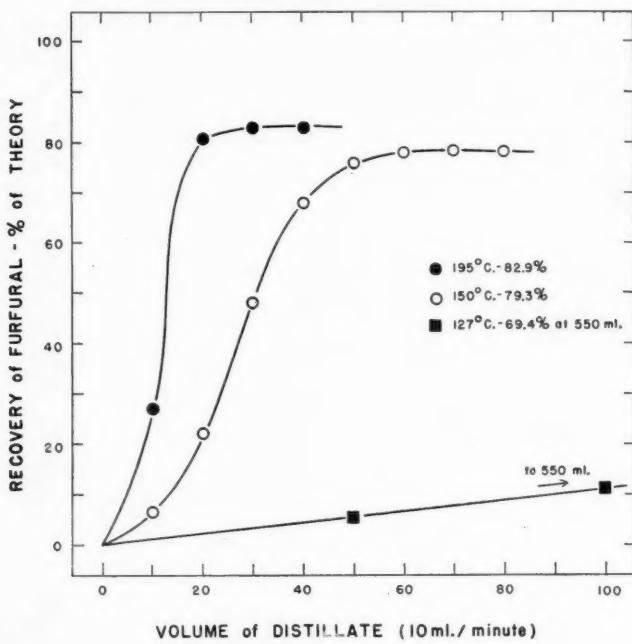


FIG. 3.

min. of distillate, 2.0 mgm. or less of the sugars can be distilled in five minutes and the spectrophotometric measurement takes perhaps another three, so that within the limits stated the method should be suitable for many purposes.

Chromatography and Sugar Mixtures

Having demonstrated that solutions of single sugars could be determined with some degree of accuracy, synthetic mixtures were prepared, separated into individuals on a paper chromatogram, and the sugars converted into furfural derivatives as before.

The requirements for this determination are (*a*) that the components of the mixture can be separated satisfactorily, (*b*) that sufficient of each is present to give a reading on the spectrophotometer, (*c*) that the solvent used to separate the sugars does not interfere, e.g., collidine, and (*d*) that no appreciable amount of carbohydrate material is extracted from the paper along with the sugar. Requirements (*a*) and (*c*) are merely cases of selecting the appropriate solvents, (*b*) would appear from the first part of this paper to allow something less than 0.1 mgm. of sugar to be determined, while (*d*) is a factor the importance of which can be reduced by running a blank on a part of the chromatogram which contains no sugar. In the present work the blanks were sufficiently small to be neglected when the steam was generated from potassium permanganate solution and an all-glass apparatus was used. The results for several mixtures are given in Table II.

TABLE I
YIELD OF FURFURAL DERIVATIVES FROM SUGARS†

Sugar	Amount, mgm.	Volume of distillate, cc.	No. of determinations	Average yield, %	Mean deviation	Maximum deviation
Xylose	20	100	5	88.9	± 1.8	2.8
	10	100	5	89.9	± 1.3	1.9
	2	50	10	91.0	± 1.7	1.9
	1	50	5	91.2	± 1.2	1.5
	0.5	50	10	94.1	± 2.2	2.6
	0.2	50	3	96.0	± 0.2	0.5
	0.1	50	3	102.5	± 1.1	1.2
Ribose	20	100	3	69.3	± 2.4	3.6
	2	50	3	74.9	± 1.8	1.9
	0.5	50	3	76.4	± 2.0	2.4
	0.2	50	3	77.2	± 2.3	3.7
	20	100	3	58.3	± 1.2	1.7
Arabinose	2	50	5	60.6	± 0.7	1.6
	1	50	5	61.3	± 1.8	2.5
	0.2	50	5	62.5	± 2.1	2.3
	0.05	50	3	70.3	± 1.9	3.1
	20	100	3	54.5*	± 1.7	2.9
Rhamnose	2	50	3	55.9	± 1.8	2.7
	1	50	3	59.6	± 1.4	1.6
	0.2	50	3	61.7	± 2.5	3.1
	0.1	50	3	60.8	± 1.9	2.6
	20	150	3	17.8**	± 2.5	2.8
Galactose	2	50	5	20.0	± 2.1	3.0
	0.2	50	3	19.8	± 1.8	2.4
	0.1	50	3	19.6	± 2.3	2.5
	20	100	4	13.7**	± 1.5	2.6
	2	50	7	15.5	± 1.2	3.2
Glucose	1	50	5	15.6	± 0.7	0.9
	0.2	50	5	15.5	± 1.1	1.4
	0.1	50	3	16.4	± 1.3	2.4
	0.05	50	3	15.6	± 2.6	3.5

* 5-methylfurfural
** 5-hydroxymethylfurfural

† 5 ml. 85% phosphoric acid in oil bath at 195°C.
with steam at rate of 10 ml. per min.

TABLE II
ANALYSIS OF SUGAR MIXTURES

Developing solvent	Sugar mixture	Present, mgm.	Found,* mgm.			
			(Average)			
Butanol-water	Xylose	0.50	0.47	0.47	0.47	0.47
	Glucose	0.50	0.50	0.45	0.46	0.47
Ethyl acetate - acetic acid - water 3 : 3 : 1	Xylose	0.50	0.49	0.50	0.47	0.49
	Glucose	0.50	0.44	0.48	0.44	0.45
	Galactose	0.50	0.45	0.56	0.49	0.50
	Rhamnose	0.50	0.41	0.43	0.40	0.41
Butanol-water	Xylose	0.50	0.48	0.49	0.48	0.48
	Glucose	0.50	0.48	0.46	0.49	0.48
	Arabinose	0.50	0.53	0.48	0.49	0.50

* Based on factors given in Table I.

The three determinations made with each mixture show fair agreement, but in most cases indicated smaller amounts of sugar than had been put on the paper. Rhamnose was particularly poor in this respect. The reason for this apparent loss of sugar probably lies in the 'tailing' that occurs during chromatographic separation, causing losses when the 2 1/2 in. strip is cut out. It would seem likely that this is also responsible for the results being less reproducible than when using pure sugars. This shortcoming, however, is connected with the particular method of chromatography and not with the subsequent extraction and determination of the sugar. Having separated a mixture of sugars on a paper chromatogram, the present work offers an alternative means of determining each, within the limits of error given by other methods.

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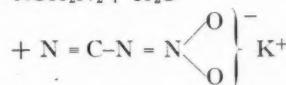
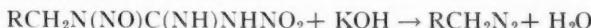
DIAZOHYDROCARBONS¹

BY A. F. MCKAY, W. L. OTT,² G. W. TAYLOR,²
M. N. BUCHANAN,³ AND J. F. CROOKER

Abstract

1-Substituted-1-nitroso-3-nitroguanidines on treatment with aqueous potassium hydroxide solution give diazohydrocarbons. This method has been used to prepare diazomethane, diazoethane, diazo-*n*-propane, diazo-*n*-butane, diazo-*n*-pentane, and phenyldiazomethane. Potassium nitrocyanamide has been isolated as a by-product of this reaction.

A method was described (11) for the preparation of diazomethane from the intermediate 1-methyl-1-nitroso-3-nitroguanidine. This procedure has been extended to include some of the higher diazohydrocarbons and the by-product, potassium nitrocyanamide, isolated. The general reaction may be formulated as follows:



R = H, CH₃, C₂H₅, C₃H₇, C₄H₉, or phenyl.

Diazomethane prepared in this manner has been obtained in 83–93% yield. The yields of diazoethane, diazo-*n*-propane, diazo-*n*-butane, and diazo-*n*-pentane reported in Table I are lower but of the same order as those obtained with the corresponding N-nitroso-N-alkyl urethanes (15) and nitrosoalkyldiacetonamines (1). Wilds and Meader (15) have increased the yield of diazoethane from N-nitroso-N-ethylurethane to 75% by a modification of the usual procedure (2).

Attempts to prepare diazoisopropane and diazocyclohexane by the present method were unsuccessful. Although 1-isopropyl-3-nitroguanidine (5) and 1-cyclohexyl-3-nitroguanidine (12) are easy to prepare, these compounds could not be converted to the nitrosamines (13). In general any derivative of nitroguanidine possessing a secondary carbon attached to the amino group has not given a nitroso derivative under the usual conditions of nitrosation.

Phenyldiazomethane, first reported by Hantzsch and Lehmann in 1902 (7), was prepared in 74% yield as a red oil from the addition of 1-benzyl-1-nitroso-3-nitroguanidine to aqueous potassium hydroxide solution. The oil was separated from the aqueous phase and washed with water before or after solution in ether. It was found that the addition of benzylnitrosonitroguanidine to potassium hydroxide solution covered with ether lowered the yield (23–30%) considerably.

¹ Manuscript received July 24, 1950.

Contribution from Defence Research Chemical Laboratories, Ottawa, Ontario, and Department of Chemistry, Queen's University, Kingston, Ontario. Issued as DRCL Report No. 50.

² Recipients of Grants-in-aid from Defence Research Board, Canada.

³ Recipient of Grant-in-aid from Richardson Science Fund, Queen's University.

During the alkaline decomposition of alkylnitrosonitroguanidines a white solid appeared at the ether-water interface. A number of runs were performed in which the ethereal diazohydrocarbon was not recovered by distillation but the mixture filtered. In this manner the white solid was obtained and purified to a constant melting point of 135–136°C. It gave a positive test (6) for the nitramino group and exploded when heated above its melting point on a spatula. The analytical values were in good agreement with those calculated for potassium nitrocyanamide. Occasionally the crude potassium nitrocyanamide changed to a high melting (238°C.) solid. The reactions of the potassium salt of nitrocyanamide will be described in a later paper. The original filtrate was separated into ethereal and aqueous fractions and the ethereal fraction washed with water. The diazohydrocarbon content was determined by the titration technique of Marshall and Acree (10). These results are recorded in Table I.

The alkylnitrosonitroguanidines are all solids and have been stored in brown bottles on the laboratory stock shelves for a year and a half without deterioration. They provide a convenient source of the diazohydrocarbons. This is the main advantage in using alkylnitrosonitroguanidines. The over-all yields of the higher diazohydrocarbons from nitroguanidine are low and this may offset the convenience of stability of the intermediates. However, the various steps in the production of diazomethane from nitroguanidine have been modified to give consistently good yields. Thus the procedure for the preparation of diazomethane is given in detail in the experimental section.

Within the past two years some 15 lb. of the various alkylnitrosonitroguanidines has been prepared and used in various reactions. This work has been conducted in fumehoods with good draft, and no harmful effects were noted. At first, ample precautions were not taken and varying degrees of skin irritation were experienced (11). This skin irritation is more severe with contamination resulting from the preparation and use of the higher alkylnitrosonitroguanidines. Thus these compounds should be treated as noxious agents and due precautions observed.

Experimental*

Diazomethane from Nitroguanidine

1-Methyl-3-nitroguanidine

A solution of 66 gm. (1.18 mole) of potassium hydroxide was placed in a liter beaker and 104 gm. (1 mole) of nitroguanidine was added with stirring. Then 64.2 gm. (0.91 mole) of methylamine hydrochloride was added with efficient stirring. The temperature of the reaction mixture was raised to 53°C. over a period of 10 min. and maintained at $51 \pm 2^\circ\text{C}$. for a further period of 25 min. After the first 20 min. of heating an extra 15 gm. (0.22 mole) of methylamine hydrochloride was added. At the end of the heating period the

* All melting points are uncorrected.

reaction mixture was cooled and the heavy white precipitate removed by filtration and washed with water. The yield of crude product varied from 86 to 91 gm. (72.9–77%) and melted at 155–159°C.† The crude product was refluxed for a short time with 550–570 cc. of 95% ethanol and the hot solution filtered. On cooling to room temperature, crystals separated; these were collected by filtration and washed with cold ethanol. The filtrate was concentrated to approximately 80 cc. and allowed to cool to room temperature, whereupon a second crop of crystals separated. The combined yield of purified methylnitroguanidine was 73–80.3 gm. (62–68%), and the product melted at 159–161°C.

1-Methyl-1-nitroso-3-nitroguanidine

The method of preparing 1-methyl-1-nitroso-3-nitroguanidine has been described (12) in detail.

Diazomethane

The yield of diazomethane from 1-methyl-1-nitroso-3-nitroguanidine has been increased to 83–93% by the following modification in procedure.

Methylnitrosonitroguanidine (0.26 mole) is added portionwise over a period of *ca.* 10 min. to a solution of 38 gm. of potassium hydroxide in 76 cc. of water covered with 250 cc. of ether and cooled to –4°C. During the addition of methylnitrosonitroguanidine the reaction mixture is swirled. The flask is then connected to the distillation apparatus assembled as described by Arndt (2). The receivers are placed in a dry-ice-acetone bath and maintained at –20° to –30°C. The ethereal diazomethane solution is distilled over within a period of 20 to 35 min.

1-Substituted-2-nitroguanidines

Ethyl- and *n*-butylnitroguanidines were prepared as previously described (12). *n*-Propyl-, *n*-pentyl- and benzylnitroguanidines were prepared in 50–60% yields by the method of Davis and coworkers (4, 5).

1-n-Propyl-1-nitroso-3-nitroguanidine

n-Propylnitroguanidine (71.7 gm.; 0.491 mole) was dissolved in 158 cc. of nitric acid (sp. gr. 1.42) and diluted with 200 cc. of water. The nitrosation was conducted in the same way as described (12) for the nitrosation of ethyl-nitroguanidine. A 73% yield of product (m.p. 109°C. with decomp.) was obtained. One crystallization from methanol (3.5 cc. per gm.) gave a 69.4% yield of 1-*n*-propyl-1-nitroso-3-nitroguanidine melting at 118°C. with decomp. Calc. for C₄H₉N₅O₃: C, 27.4; H, 5.14; N, 40.0%. Found: C, 27.3; H, 5.10; N, 39.6%.

† To prepare 1-methyl-1-nitroso-3-nitroguanidine, it is unnecessary to recrystallize the crude methylnitroguanidine. The crude product can be nitrosated immediately without loss of yield or purity of product (3).

1-Benzyl-1-nitroso-3-nitroguanidine

Ten grams (0.516 mole) of benzylnitroguanidine was dissolved in 165 cc. of nitric acid solution and diluted with 100 cc. of water. The nitrosation was carried out as above by adding 2 mole equivalents of sodium nitrite dissolved in 20 cc. of water. At the end of the reaction, which was carried out at 14°C., the yellow 1-benzyl-1-nitroso-3-nitroguanidine (m.p. 114.5–115°C. with decomp.) was removed by filtration and washed well with water. This crude product obtained in 69% yield was purified by crystallizing from methanol. The melting point of the purified product was 117.5–118°C. with decomp. Calc. for $C_8H_9N_5O_3$: C, 43.00; H, 4.04; N, 31.40%. Found: C, 42.92; H, 4.00; N, 31.22%.

*Preparation of Higher Diazohydrocarbons**A. Distillation Method*

The distillation technique used in the preparation of diazomethane was employed for the preparation of the higher diazohydrocarbons. In some of the runs, other solvents were substituted in place of ether. The results are tabulated in Table I.

TABLE I
PREPARATION OF DIAZOHYDROCARBONS

Diazohydrocarbon	Solvent	Yields, %	
		Distillation method	Filtration method
Diazoethane	Ether	30–49.2	56–65.7
	Ether Pet. ether (41–51°C.)	49.4–52.6	
Diazo- <i>n</i> -propane	Pet. ether (30–60°C.)	33.2–42.4	55.0–60.7
	Ether	33–49.2	
Diazo- <i>n</i> -butane	Ether	33–49.2	57.6–64.0
	<i>n</i> -Heptane Pet. ether: <i>n</i> -heptane (1:1)	34.0 35.4–45.3	
Diazo- <i>n</i> -pentane	Ether		56.7–58.0

B. Filtration Method

All the glassware used in the following experimental procedure was cooled to 0° to –4°C. previous to use.

A solution of 22.4 gm. (0.40 mole) of potassium hydroxide in 22.4 cc. of water was covered with 250 cc. of freshly distilled ether and cooled to –4°C. Then the 1-alkyl-1-nitroso-3-nitroguanidine (0.1 mole) was added portionwise to the reaction flask over a period of five to seven minutes. During the addition of the nitroso compound, the reaction mixture was swirled vigorously. The solid by-product, which separated at the solvent interface, was filtered from the reaction mixture and the ether layer separated in a separatory funnel.

The ethereal fraction was then washed with water (2×200 cc.) and dried over pellets of potassium hydroxide or used without drying. The estimation of diazohydrocarbon content of the *undried* ethereal solution was determined by the titration technique of Marshall and Acree (10).

The solid by-product (m.p. 130–134°C.) was washed several times with ether. If care is not taken to keep this compound covered with ether, it takes up moisture from the air and changes into a high melting substance. The compound, saturated with ether, was transferred to a flask, using absolute alcohol or 95% ethanol. It was crystallized from ethanol to give well defined crystals melting at 135–136°C., yield 60.8–65%. It explodes when heated above its melting point on a spatula. This compound gives a positive nitramine test (6). The purified material is quite stable even on exposure to the air over prolonged periods of time. Calc. for CN_3O_2K : C, 9.58; N, 33.6; K, 31.2%. Found: C, 9.66; N, 33.86; K, 31.2%.

Phenyldiazomethane

Five grams (0.022 mole) of 1-benzyl-1-nitroso-3-nitroguanidine was added portionwise to a stirred solution of 21 gm. (0.037 mole) of potassium hydroxide in 30 cc. of water. The reaction was run at room temperature. A red oil separated which was removed in a separatory funnel, washed with water (3×20 cc.), and dried over potassium hydroxide pellets.

The yields (74–76%) were determined by dissolving the washed oil in ether, adding an excess of standard ethanolic hydrogen chloride, and back-titrating with standard alkali.

Characterization of Diazohydrocarbons

The diazohydrocarbons were characterized as the 3, 5-dinitrobenzoates. An ethereal solution of excess 3, 5-dinitrobenzoic acid was added to the ethereal diazohydrocarbon solution at 0°C. After the reaction was complete, the excess acid was removed by extracting the ether solution with 5% potassium carbonate solution. The ether solution was washed with water, dried over anhydrous potassium carbonate and evaporated to dryness. The crude 3, 5-dinitrobenzoates were obtained in 95–99% yield and melted a few degrees low. They were purified by crystallizing from 95% ethanol. The 3, 5-dinitrobenzoates prepared in this manner are listed in Table II.

TABLE II
3, 5-DINITROBENZOATES

3,5-Dinitrobenzoate	M.p. °C.	
	Found	Reported
Ethyl	91–92	93–94 (14)
n-Propyl	72.5–73.5	74–75 (14)
n-Butyl	61–61.5	61–63 (14)
n-Pentyl	45–45.5	45–46 (9)
Benzyl	112.5–113	113 (8)

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THE PREPARATION OF 1-ALKOXY-1,3-BUTADIENES BY PYROLYSIS OF TRIALKOXYBUTANES

II. CIS- AND TRANS-1-METHOXY-*, 1-ETHOXY-, AND 1-*n*-PROPOXY-1,3-BUTADIENES¹

BY CHARLES G. FARNILO AND R. V. V. NICHOLLS

Abstract

The acetals, 1,1,3-trimethoxybutane, 1,1,3-triethoxybutane, and 1,1,3-tri-*n*-propoxybutane have been pyrolyzed by passage over a synthetic barium silicate at various temperatures. The yields of the 1-alkoxy-1,3-butadienes isolated from the products of pyrolysis were 80, 45, and 36% respectively. A limited number of catalysts of compositions varying from BaO: 2SiO₂ to BaO: 10SiO₂ have been prepared, including the recommended, BaO: 5SiO₂. The qualitative effect of catalyst composition of some of these silicates on the yield of 1-methoxy-1,3-butadiene has been described. *trans*-1-Methoxy-1,3-butadiene has been isolated and characterized by means of reactions with maleic anhydride, and a solution containing *cis* and *trans* molecules has been analyzed and shown to contain 60% *cis*-1-methoxy-1,3-butadiene.

Introduction

Wichterle (10) first prepared 1-alkoxy-1,3-butadienes by means of a liquid-phase decomposition of 3-chloro-1,1-dialkoxy-butanies using fused potassium hydroxide to remove the hydrogen chloride and alcohol molecules and to introduce the double bonds in the 1 and 3 positions. The dienes prepared were ethoxy-, *n*-propoxy-, *n*-butoxy-, and isobutoxy-1,3-butadienes, but the yields (10%) were extremely low and variable, nor could 1-methoxy-1,3-butadiene be prepared by this method.

Meier (6) reported the first use of a gas-phase method for producing 1-methoxy-1,3-butadiene by pyrolysis of 1,1,3-trimethoxybutane using a catalyst of composition BaO: 5SiO₂. His description of the preparation of the catalyst is very incomplete and insufficient for the duplication of his results. Marion and Farmilo (4) described a technique that would produce a catalyst, varying in composition from BaO: 4SiO₂ to BaO: 5SiO₂, by which conversion yields of 40 to 50% 1-methoxy-1,3-butadiene could be obtained. A further study of the conditions of this pyrolysis reaction has been made, and the reaction has been extended to the cracking of two higher homologues. Certain results were obtained which qualitatively indicate the effect of varying catalyst composition upon these dealcoholations.

* Only the geometrical isomers of 1-methoxy-1,3-butadiene were studied.

¹ Manuscript received in original form December 18, 1949, and, as revised, June 22, 1950. Contribution from the Department of Chemistry, McGill University, Montreal, Que. The material in this paper is a portion of a thesis submitted by C. Farmilo to the Graduate Faculty, McGill University, Montreal, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Present address: Organic Chemistry and Narcotic Section, Food and Drugs Division, Department of National Health and Welfare, 35 John Street, Ottawa, Ont.

Experimental

Preparation of 1,1,3-Trialkoxybutanes

These materials were prepared by the method proposed by Meier (5) which consists in general of the condensation of an alcohol with crotonaldehyde in the presence of small amounts of hydrochloric acid as a catalyst. The crotonaldehyde used in these experiments was obtained from Shawinigan Chemicals Limited, Shawinigan Falls, Quebec. This commercial crotonaldehyde had the following constants: b.p. 98.0°C. (760 mm.), d_4^{15} 0.8575, and n_D^{20} 1.4340; and after drying over anhydrous sodium sulphate and distillation, the following constants were found: b.p. 102.5°C. (750 mm.), d_4^{20} 0.8575, $n_D^{17.5}$ 1.4335. These are compared with the physical constants given in the Handbook of Chemistry and Physics (Chemical Rubber Co.): b.p. 104–105°C. (102.4°C.) (760 mm.), d_4^{15} 0.8575, $n_D^{17.5}$ 1.43838.

1,1,3-Trimethoxybutane

Methanol (5 liters), acidulated with 12 M hydrochloric acid (120 ml.), was added to a 10 liter round bottomed flask, containing crotonaldehyde (1.5 liters). The flask, equipped with a reflux condenser, was placed in a water bath at 50°C. for 24 hr. The resulting yellow solution was cooled and neutralized with fresh, solid calcium hydroxide. The end point of the neutralization reaction was determined by the use of pH paper and was observed to coincide with the point at which finely divided excess calcium hydroxide remained suspended in the solution after stirring. Prior to the end point the unreacted calcium hydroxide settled out rapidly. The supernatant liquor was siphoned through a large Büchner filter to remove solid calcium hydroxide and calcium chloride. Excess methanol was removed from the solution at reduced pressure.

The residue was fractionally distilled. The forerun had a boiling range 20–30°C. (15 mm.) and refractive index $n_D^{25.2}$ 1.3540. The desired trimethoxybutane distilled at 55°C. (15 mm.) and was obtained in 75% yield. This material was shaken with 10% aqueous sodium bisulphite and the acetal was refluxed with sodium metal until the evolution of hydrogen had ceased. These steps removed traces of crotonaldehyde, alcohol, and water. The acetal was then stored over sodium metal. The physical constants of 1,1,3-trimethoxybutane were: b.p. 157.0°C. (760 mm.), 153.0°C. (740 mm.), 55.0°C. (16 mm.), 42.0°C. (7 mm.); d_4^{25} 0.9160; n_D^{12} 1.4063, n_D^{19} 1.4039. After treatment with sodium the acetal had a refractive index of n_D^{25} 1.4016.

1,1,3-Triethoxybutane

Ethanol (4 liters) containing hydrochloric acid (120 ml.) was added to crotonaldehyde (1 liter). The solution was allowed to react at 50°C. for 24 hr. After neutralization with calcium hydroxide, the ethanol was removed by distillation. The resulting mother liquor on cooling deposited a crystalline material (30 gm.). On fractional distillation of the filtered liquid a forerun (500 ml.) with these physical constants, b.p. 90.0°C. (25 mm.) and n_D^{26} 1.3939,

was obtained. The yield of required acetal which boiled at 85.6°C. (18 mm.) was 60%. The physical constants of the liquid after treatment with sodium were as follows: b.p. 190.0°C. (760 mm.), 85.6°C. (18 mm.), 95°C. (24 mm.); d_4^{20} 0.8765; n_D^{25} 1.4080. These constants were identical with those reported by Meier (*loc. cit.*).

1,1,3-Tri-*n*-propoxybutane

Propanol-1 (1300 ml.) was added to crotonaldehyde (325 ml.) containing 12 M hydrochloric acid (16.2 ml.) and allowed to react at 50°C. for 24 hr. After neutralization with calcium hydroxide and filtration the liquid was fractionated by distillation under reduced pressure to avoid decomposition. The product contained propanol and a liquid whose properties were identical with those given by Meier (*loc. cit.*) for 1,1,3-tri-*n*-propoxybutane. The acetal was obtained in 30% yield and had these physical constants: b.p. 230°C. (760 mm.), b.p. 110–115°C. (5–10 mm.), d_4^{25} 0.8575, n_D^{25} 1.4232. The molecular refractivity calculated was 67.06 and found to be 68.90 using the measured constants.

Unsuccessful attempts were made to synthesize 1,1,3-triisopropoxybutane and 1,1,3-tri-*n*-butoxybutane by the method used for the corresponding methoxy-, ethoxy-, and *n*-propoxybutanes. However, from the crotonaldehyde-butanol reaction mixture an acetal was isolated. One fraction had the following physical constants, b.p. 155°C. (30 mm.), d_4^{20} 0.8720, $n_D^{19.5}$ 1.4335. The molecular refractivity found for $C_{12}H_{24}O_2$ is 59.5 and the calculated molecular refractivity for 1,1-dibutoxybutene-2 is 60.4. This material was assumed to be 1,1-dibutoxybutene-2 on this basis and no further work has been done on the proof of the structure of this compound.

Preparation of Barium Silicate Catalysts

Table I shows the commercially available sodium silicates* which were used in the preparations reported in Table II.

TABLE I
COMMERCIAL SILICATES, SHOWING RATIO OF SODIUM OXIDE TO SILICON DIOXIDE

National Silicate name*	Weight % Na_2O	Weight % SiO_2	Molar ratio $Na_2O : SiO_2$
Metso Brand	29.5	28.2	1:1
C—Brand	18.0	36.0	1:2
N—Brand	8.9	28.7	1:3.3
S—Brand	6.3	24.6	1:4
S—Special Brand	6.8	25.3	1:4.2

The method of preparation of the catalyst, $BaO : 5SiO_2$, described by Marion and Farmilo (4) has been simplified, peptization and dialysis being omitted in the following procedure. S-brand sodium silicate (93 ml., 108 gm.)

* Special thanks are due to Mr. L. A. Richardson, Assistant Manager, National Silicates Limited, New Toronto, Ontario, for the supply of silicates used in the preparation of catalysts and for his kind advice during this work.

was dissolved in distilled water (1 liter), and barium chloride (20.8 gm.) dissolved in the least amount of water was added slowly to the stirred silicate. Immediate flocculation occurred. The material was allowed to digest overnight with stirring, then filtered, washed with water, dried at 110°C. and analyzed. For analysis a small sample (0.5 gm.) of the oven-dried material was placed in a weighed platinum crucible, then dried to constant weight by heating over a blast burner. A small amount (three drops) of concentrated sulphuric acid was then added and about 5 ml. of hydrofluoric acid. The liquid was then heated and finally fumed to dryness over a blast burner. When cool the crucible was weighed and the amount of the barium oxide calculated from the weight of barium sulphate. The silicon dioxide was obtained by difference. Duplicate samples were analyzed and the results averaged. These results for methods of preparation under various conditions are shown in Table II.

TABLE II

EFFECT OF CONDITIONS OF PREPARATION ON COMPOSITION OF BARIUM SILICATE CATALYSTS

Method	Run No	Effect of	Conditions of preparation	Analysis		
				BaO, %	SiO ₂ , %	Ratio BaO: SiO ₂
1	38-RO	Mechanical mixing	Attempt to duplicate Meier's catalyst	17.92	80.32	1: 11.6
2	38-I	Mechanical mixing	Same as 38-RO Meier's claim	33.87	66.13	1: 5.0
3	70-I	Peptization and dialysis	Direct addition of BaO ₂ and Na ₂ O: x SiO ₂ in aqueous solution, with stirring	37.44	60.44	1: 4.12
4	41-RI	Silicate brand	Waterglass brand Na ₂ O: SiO ₂ precipitated with Ba(NO ₃) ₂	47.6 46.4	52.4 53.6	1: 2.9
5	44-RI	Silicate brand	N-Brand Na ₂ O: SiO ₂ precipitated with BaCl ₂	39.1 42.2	60.9 57.8	1: 3.7
6	51-RI	Dilution	S-Brand Na ₂ O: SiO ₂ (76.7 gm.) in water (1.5 liters) + BaCl ₂ (53 gm.) in water (4 liters)	38.8 38.9	61.2 61.1	1: 4.02
7	55-RI	Dilution	S-Brand Na ₂ O: SiO ₂ (606.6 gm.) in water (4 liters) + BaCl ₂ (440 gm.) in water (2 liters)	40.0 41.5	60.0 58.5	1: 3.7
8	84-RI	Reaction time	S-Brand Na ₂ O: SiO ₂ (30.8 gm.) in water (1 liter) + BaCl ₂ (20 gm.): reaction time, 24 hr.	35.4 35.5	65.6 65.5	1: 4.7
9	88-RI	Reaction time	S-Brand Na ₂ O: SiO ₂ (30.8 gm.) in water (1 liter) + BaCl ₂ (20 gm.): reaction time, 4 hr.	40.6 40.5	59.4 59.4	1: 3.6
10	92-RI	Acid treatment to cause gelation	S-Brand Na ₂ O: SiO ₂ (83 ml.) + H ₂ O (2 liters) + H ₃ PO ₄ (24 gm.) + BaCl ₂ (28 gm.) in H ₂ O (100 ml.) + Na ₂ O: SiO ₂ (95 ml.) gel.	20.8 20.5	79.14 79.15	1: 10.0
11	52-RI	Acid treatment of precipitate	BaO: 1.7 SiO ₂ (110 gm.) + conc. HCl (1 ml.) + 12 hr. extraction + wash + peptization (NH ₄ OH) + dialysis to remove NH ₄ ⁺	0.20 0.22	99.79 99.78	1: 1600

It was found that using the directions given by Meier (6) a barium silicate having the composition $\text{BaO}: 5\text{SiO}_2$ could not be obtained. In Table II, results of an analysis of material prepared following Meier's directions are given under Method I; the ratio of barium oxide to silicon dioxide was found to be 1: 11.6. A direct precipitation method was then used for the preparation of barium silicates similar to that reported previously (*loc. cit.*). Analytical results for catalysts prepared by this precipitation method are reported under Methods 3 to 11, Table II. The methods reported here illustrate conditions suitable for producing catalysts of the range of molecular compositions of barium oxide and silicon dioxide given by $\text{BaO}: x\text{SiO}_2$, where x is approximately 2,3,4,5,10,12, and 1600.

Acetal Pyrolysis Apparatus

The apparatus shown in Fig. 1 was comprised of five units labeled in the figure *A*, *B*, *C*, etc. The liquid-feed input system (*A*) was capable of delivering small amounts (0.25 ml. per min.) at a constant rate (with occasional checking) for the length of times required. This control of the feed rate was facilitated by the use of a precision rotameter. The pyrolysis system (*B*) consisted of a Pyrex glass tube 20 mm. inside diameter and 100 cm. in length and was electrically heated by means of two separate resistance-wire coils controlled by variable voltage transformers. The preheater (void) and vaporizer, filled with glass helices, comprised the first 50 cm. of the tube and were maintained at a temperature about 50°C. higher than that of the barium silicate catalyst bed to cause complete vaporization of the reactant. The barium silicate was 4½ mesh grain size, and about 300 cc. (25 gm.) was used. It was found that a 50°C. temperature gradient existed throughout this catalyst bed. Hence temperature ranges are reported (Fig. 2) for the pyrolysis reaction rather than the exact temperatures measured at any one point in the catalyst. An even temperature gradient was obtained through the catalyst, and temperatures at all points were measured by means of a sliding thermocouple labeled *E*. The flow of the gaseous acetal was maintained by means of a carrier gas, in this case nitrogen. A constant flow of purified gas (system *C*) was passed through the pyrolysis system to carry the reactants and products of pyrolysis into the collection system labeled *D*. The product-free gas was then metered (25 liters per hr.) before passing to the atmosphere.

Run Procedure

The reactant was pumped into the calibrated reactant reservoir through a side arm by lowering this reservoir mercury level. A constant nitrogen tank pressure, 10 p.s.i., was maintained on the surface in the mercury reservoir to obtain a constant feed rate into the pyrolysis furnace. At the rate chosen and a constant carrier gas flow rate the reactant acetal was fed into the pyrolysis tube and the products collected for the period of the run. The product trap and additional trap were cooled by immersion in Dewar flasks containing dry-ice - acetone cooling mixture.

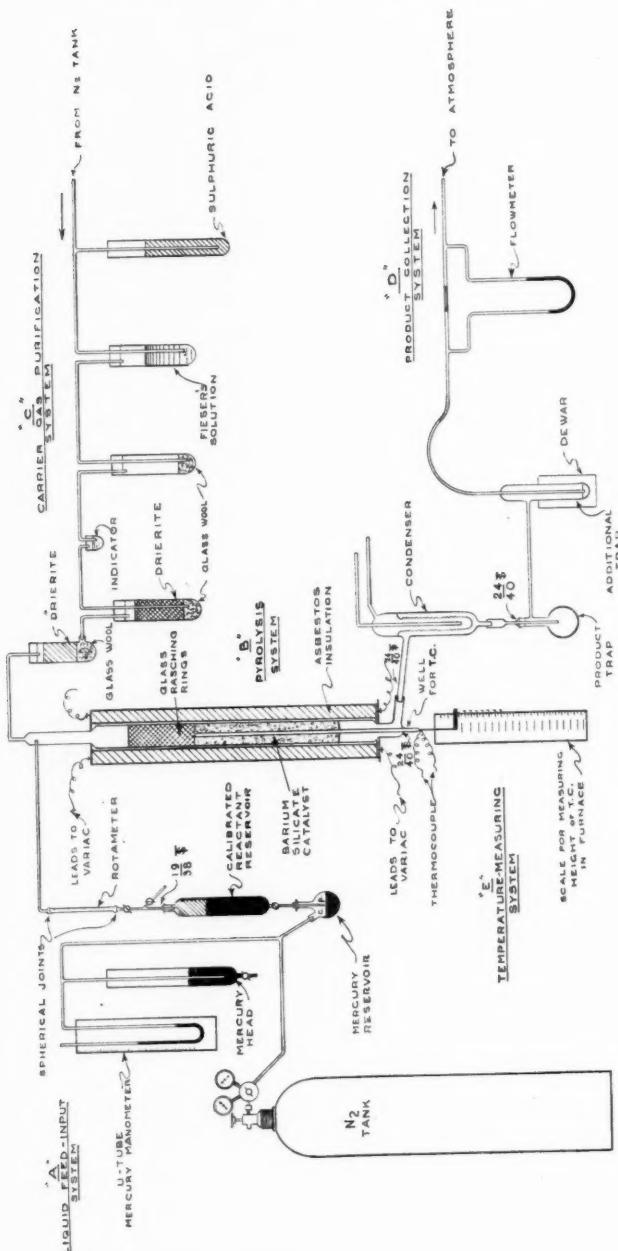


FIG. 1. Acetal pyrolysis apparatus.

1-Methoxy-1,3-butadiene

The products of the pyrolysis of 1,1,3-trimethoxybutane were weighed and washed with water to remove methanol. The remaining liquid was then dried over anhydrous sodium sulphate and roughly fractionated by simple distillation. The fractions usually obtained, depending on the catalyst composition and other conditions, had the following boiling ranges, 60–80°C., 80–95°C., 95–125°C., and a residue whose boiling point was 147°C. Similar fractions for several experiments with the same catalyst and conditions were then combined and fractionated using a simple short unpacked column. Three fractions are described in Table III and were obtained from this distillation. Fraction 1 was found to be the azeotrope of methanol and methoxybutadiene described previously by Meier (6). Washing of this fraction with water gave a lighter than water layer which proved to be 1-methoxy-1,3-butadiene which was combined with Fraction 2. This liquid had a pungent odor and b.p. 93.5°C. (after drying over anhydrous sodium sulphate). The material was assumed to be *trans*-1-methoxy-1,3-butadiene since it formed a crystalline adduct with maleic anhydride, 3-methoxy-1,2,3,6-tetrahydrophthalic anhydride described previously (4). Further fractionation of either of Fractions 2 or 3 under nitrogen atmosphere at 760 mm. pressure, or under reduced pressure in a metal or glass packed distillation column resulted in polymerization.

TABLE III
PHYSICAL CONSTANTS OF FRACTIONS OF 1-METHOXY-1,3-BUTADIENE

Fraction No.	B.p., °C.	n_D^{20}	d_4^{20}	Molecular refractivities, M_D		Molecular exaltation, E_D
				Found	Calculated	
1	63–5	1.4308	—	—	—	—
2	92–95	1.4590	0.8320	27.40	26.00	1.40
3	122–24	1.4610	0.8487	27.50	26.00	1.50

Adduct of Maleic Anhydride and *trans*-1-Methoxy-1,3-butadiene

To a stirred solution of Fraction 2, n_D^{20} 1.4590, (16.8 gm.) in dioxane (25 ml.), previously cooled in an ice-salt bath, was added slowly a solution of maleic anhydride (20 gm.) in dioxane (100 ml.). The reaction flask was fitted with a condenser and thermometer after the completion of maleic anhydride addition. The contents was refluxed for two hours. The flask was cooled and allowed to remain for 12 hr. at room temperature. The addition of cold water caused an oil to separate, which later became a crystalline mass. This product was digested with boiling benzene to separate any polymer that may have been formed. It was found that the entire solid material went into solution. The benzene solution was concentrated, allowed to cool, and diluted with petroleum ether, which caused 3-methoxy-1,2,3,6-tetrahydrophthalic anhydride, m.p. 99°C., to crystallize. On the basis of formation of a pure

compound the amount of adduct should have been 36.4 gm. The weight of adduct obtained was 33.85 gm. The amount of *trans*-isomer present (assuming complete reaction with maleic anhydride and complete recovery of the adduct) in the original material was 93%.

Polymerization of cis-1-Methoxy-1,3-butadiene

Fraction 3 was thought to contain *cis*-1-methoxy-1,3-butadiene, since it did not yield a crystalline adduct on the addition of maleic anhydride, but under these conditions it polymerized. The following preliminary experiment was performed to determine the total amount of diene (*cis* + *trans*) contained in the fraction, since the material had a boiling point (122°C.) considerably higher than that of either Fraction 1 or 2.

A small amount of material from Fraction 3 (0.8411 gm.) was added to a previously weighed bottle fitted with a ground-glass stopper, and cooled; maleic anhydride (0.9800 gm.) was added slowly as finely ground solid to prevent a rapid temperature rise. The flask and contents (weight 30.2428 gm.) was heated at reduced pressure (1 mm.) at 50°C. for several hours and subsequently weighed (30.2223 gm.). The loss of weight was 0.0205 gm. or 2.44% of the weight of Fraction 3 used in the experiment. The material in Fraction 3 was calculated to contain, on the basis of this reaction, 97.6% diene.

A larger amount of Fraction 3 (12 gm.) was added to maleic anhydride (14 gm.) in dioxane using the method described above. The product (12.1 gm.) was treated as above to separate amorphous polymer (7.2 gm.) and crystalline adduct (4.9 gm.). Fraction 3 contained about 60% of *cis*-1-methoxy-1,3-butadiene.

1-Ethoxy-1,3-butadiene

This material was prepared by a method similar to that used for preparing 1-methoxy-1,3-butadiene. The products from the pyrolysis of 1,1,3-triethoxybutane (165 gm.) were weighed, and washed with water, the residue (8.41 gm.) was dried over anhydrous sodium sulphate and then fractionated by a simple distillation into a Fraction 1 (6.2 gm.) boiling between 65° and 100°C. and a second fraction (20.0 gm.) distilling between 108° and 110°C. and a third fraction (10.0 gm.) between 110° and 115°C. Fractions 2 and 3 were combined and redistilled to yield a liquid (25 gm.), which boils at 112°C. (760 mm.), $n_{D}^{25.5}$ 1.4550. The yield of crude material obtained from this run was 45.6%. This compares with a yield of less than 10% of a similar material described by Wichterle (10) as having the following physical constants: b.p. 112.5–115°C., d_{4}^{20} 0.8205, n_{4}^{20} 1.4610. There was no attempt made to separate this diene into its *cis*- and *trans*- isomers.

1-n-Propoxy-1,3-butadiene

The reactant, 1,1,3-tri-*n*-propoxybutane (90 cc.), was pyrolyzed by passage over a barium silicate catalyst of composition BaO: 5SiO₂ at a temperature

between 300° and 350°C. and the products (57.3 gm.) which were washed with water and dried over anhydrous sodium carbonate yielded several fractions, with the following boiling point ranges: (1) 75–85°C.; (2) 90–100°C.; (3) 100–110°C.; and (4) 130–135°C. Fraction 4 (12.37 gm.) was again washed and dried then redistilled to yield a liquid (10.0 gm.) with a penetrating odor and b.p. 134°C. (757 mm.), d_4^{29} 0.8360, n_D^{20} 1.4640. Molecular refractivity found 36.9; calc., 37.4. The physical constants compare with those given by Wichterle (10) for the same compound. The yield of pure 1-*n*-propoxy-1,3-butadiene obtained from the experiment was 36% as compared with 4% obtained by Wichterle.

Results and Discussion

Preparation of Alkoxybutanes

An attempt was made to determine the extent of applicability of the Meier reaction (5) for the preparation of 1,1,3-trialkoxybutanes, by the direct addition of several alcohols to crotonaldehyde in the presence of hydrochloric acid as a catalyst. The yields of 1,1,3-trimethoxy-, 1,1,3-triethoxy-, and 1,1,3-tri-*n*-propoxybutanes obtained by this reaction were 80, 60, and 30% respectively. Under the conditions described, butanol did not yield a tributoxybutane with crotonaldehyde but formed a normal acetal. The Meier reaction was found thus to be limited to the primary alcohols, methanol, ethanol, and propanol-1.

Pyrolysis of 1,1,3-Trialkoxybutanes

All of the experiments shown in Fig. 2, which illustrates the relation between rate of input of trimethoxybutane and the percent yield of 1-methoxybutadiene were performed using a catalyst of composition BaO: 5SiO₂. It was found that at a given feed rate an increase in temperature caused reduction in the yield of 1-methoxy-1,3-butadiene. In addition to the diene, methanol and

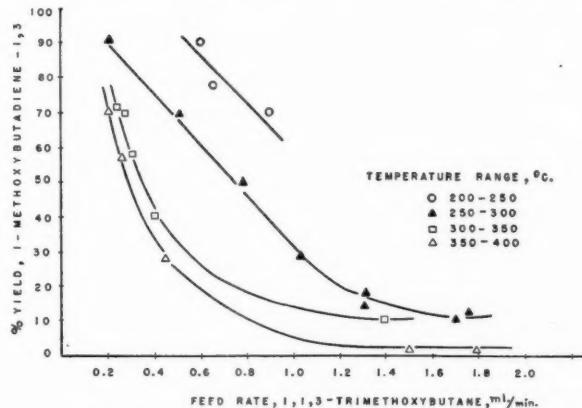
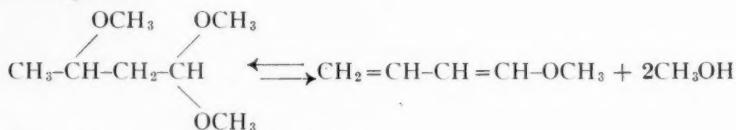


FIG. 2. Yield data for preparation of 1-methoxybutadiene.

trimethoxybutane were products of these pyrolysis reactions. Crotonaldehyde was not isolated. It was inferred from these results that the pyrolysis of trimethoxybutane under the above conditions can be represented by an equilibrium equation



and that this reaction is exothermic.

With similar conditions of feed rate, temperature of pyrolysis, carrier gas-flow-rate, and catalyst composition three alkoxybutanes, 1,1,3-trimethoxy-, 1,1,3-triethoxy-, and 1,1,3-tri-*n*-propoxybutane were pyrolyzed. The yields of diene from these reactions are shown in Table IV.

TABLE IV
PYROLYSIS OF ALKOXYBUTANES UNDER SIMILAR CONDITIONS,
SHOWING PER CENT YIELD OF ETHER

Alkoxybutane	Feed rate, ml./min.	Catalyst temp., °C.	Product	Yield, %
1,1,3-Trimethoxybutane	0.67	270-320	*1-Methoxybutadiene-1,3	80.0
1,1,3-Triethoxybutane	0.67	270-312	*1-Ethoxybutadiene-1,3	45.6
1,1,3-Tri- <i>n</i> -propoxybutane	0.62	288-349	*1- <i>n</i> -Propoxybutadiene-1,3	36.0

* Mixtures of *cis-trans* isomers.

In addition to the factors of temperature and feed rate, the catalyst composition, that is, the molecular ratio of barium oxide to silicon dioxide in barium silicates, has a definite effect on the yield of diene-ether as well as other products. Three influences of catalyst composition are:

(1) For catalysts with the ratio $\text{BaO}:x\text{SiO}_2$, where x is between 6 and 10, results show that a pyrolysis reaction producing crotonaldehyde predominated, with a small amount of diene produced. This may indicate that a different reaction occurs on catalysts where x is greater than 5, than occurred where x is 5.

(2) Meier's method for preparing barium silicates, which involves mixing freshly precipitated silica gel and barium nitrite in the proportions required to give $\text{BaO}:5\text{SiO}_2$, gave a product having the composition $\text{BaO}:11.6\text{SiO}_2$. The catalyst caused pyrolysis of the acetal to give 30% crotonaldehyde; the remainder of the product was unchanged acetal. Similar results were obtained with a catalyst having the composition 99.78% silicon dioxide. These runs were carried out at 300-350°C. and with flow rate of acetal 1.3 ml. per min., and 35 liters per hr. of nitrogen. In other words, catalysts with a composition

BaO: x SiO₂ having x greater than 10 can cause the production of crotonaldehyde.

(3) The catalyst produced from S-Brand silicate under the conditions described in detail in the experimental section had a constant composition of about BaO: 5SiO₂, and produced the maximum yields of 1-alkoxy-1,3-butadienes. This is the recommended catalyst for the preparation of these unsaturated ethers. However, it is to be noted that within the rather wide limits of catalyst composition, varying from 4 to 10 parts of silicon dioxide per part of barium oxide, it can be shown that good yields, i.e., between 60 and 90% of 1-methoxybutadiene-1,3, have been obtained. The yield of diene-ether appears to be more sensitive to the concentration of the reactant as measured by rate of input of trimethoxybutane than it is to the catalyst composition.

Reactions of cis- and trans-1-Methoxy-1,3-Butadiene with Maleic Anhydride

Farmer and Warren (2) have shown the usefulness of a Diels-Alder reaction for the estimation of conjugated dienes in mixtures. Frank (3), Craig (1), and Robey (7) have extended the use of this reaction of maleic anhydride with mixtures of *cis*- and *trans*-1-methyl-1,3-butadienes to separate the isomers. Snyder *et al.* (9) have employed the same reaction for separation of *cis*- and *trans*-1-cyano-1,3-butadienes. Similar results were obtained by us in separating *cis*- and *trans*-1-methoxy-1,3-butadienes. A completely pure *cis*-isomer could not be isolated by fractional distillation, since a rapid polymerization occurred during the process. It has been observed in the case of the methoxybutadienes that the *trans*-isomer formed a crystalline adduct, while the *cis*-isomer reacted to produce a polymer. Frank (*loc. cit.*) has also observed the same type of reaction with the 1-methyl-1,3-butadienes. Snyder *et al.* have taken precautions to prevent polymerization in the case of 1-cyano-1,3-butadienes, and therefore no definite conclusion can be stated about the tendency of *cis*-1-cyano-1,3-butadiene to polymerize while in the presence of maleic anhydride. A mechanism for the different reactions of *cis*- and *trans*-1-substituted-1,3-butadiene molecules with maleic anhydride will be reported in a later paper.

Acknowledgments

Acknowledgment is gratefully made to Dr. Léo Marion of the National Research Laboratories in Ottawa for his kind permission to one of us (C.F.) to continue this research started in his laboratories. We wish to express our thanks to Dr. Maurice Morton (now of the University of Akron) for helpful discussions of the subject and advice during the experiments. Further, the authors wish to thank their colleagues Dr. A. M. Aiken and Dr. Leo Levi for aid in making observations. Acknowledgment is made for financial assistance from the National Research Council, granted in aid of the research.

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STUDIES ON RDX AND RELATED COMPOUNDS

I. THE DIRECT NITROLYSIS OF HEXAMINE TO RDX¹

By A. H. VROOM AND C. A. WINKLER

Abstract

Maximum yields, of about 40%, of RDX were obtained with nitric acid of all concentrations down to 88%, providing the molar ratio of nitric acid to hexamine was sufficiently high. The rate of nitrolysis increased rapidly as the molar ratio of nitric acid to hexamine was increased and continued to do so after the molar ratio was raised above that required for maximum yields. The initial rate was shown to have an upper limit, however, at very high molar ratios. An intermediate in the nitrolysis reaction was isolated and identified as 3,5-dinitro-cyclotrimethylenetrinitramine-1-nitrate (I). (I) was formed rapidly in sufficient quantities of 85 to 91% nitric acid at 0°C., but had a high rate of decomposition which was independent of both acid concentration and ratio of nitric acid to (I) with 80 to 90% nitric acid. Under nitrolysis conditions some of the hexamine was converted to products not capable of giving RDX, owing apparently to hydrolysis of precursors to (I). The activation energy for the conversion of (I) to RDX was found to be identical with that for the rate controlling step of the conversion of hexamine to RDX. This fact, together with the general kinetic behavior of (I), provided evidence that (I) was a true intermediate and that its reaction to RDX was the rate controlling step in the direct nitrolysis of hexamine. The mechanism of the over-all reaction is discussed in relation to published information concerning the constitution of concentrated nitric acid. Nitracidium ion is believed to be the active nitrolyzing agent.

Introduction

It has long been known that cyclotrimethylenetrinitramine (RDX) may be prepared by the action of cold concentrated nitric acid on hexamethylene-tetramine (hexamine) (13) or its dinitrate (12). More recently, it has been prepared by reaction between formaldehyde and ammonium nitrate in acetic anhydride, generally referred to as the Ross or McGill process (5), and also by the Bachmann or combination process (5), in which hexamine, or its dinitrate, is converted to RDX in the presence of nitric acid, ammonium nitrate, and acetic anhydride.

In this laboratory, all three reactions have been studied, together with several physicochemical aspects of RDX itself and of certain closely related compounds. Presentation of the results of these investigations is begun in the present paper with that system which appears, superficially at least, to be the simplest, i.e., the action of concentrated nitric acid alone on hexamine dinitrate.

At the time this work was started, no kinetic study of the direct nitrolysis of hexamine had been reported, although the effects of nitric acid - hexamine ratio, nitric acid concentration, and temperature had received considerable attention (8, 14).

¹ Manuscript received in original form December 17, 1948, and as revised, July 14, 1950. Contribution from the Physical Chemistry Laboratory, McGill University, with financial assistance from the National Research Council of Canada.

The work reported in this paper was done in the interval 1942-1944.

Experimental and Results

I. Influence of Nitric Acid - Hexamine Ratio on the Rate of Formation and Yield of RDX

(a) Experimental

The nitric acid generally used was light yellow in color, but gave results that agreed within experimental error with those obtained with colorless acid.

Reaction mixtures of hexamine dinitrate and nitric acid were made in 125 ml. Erlenmeyer flasks cooled to about -40°C . The dinitrate was used to avoid the highly exothermic reaction with hexamine itself. Use of the dinitrate is justified by thermochemical data which show it to be an intermediate in the direct nitrolysis of hexamine (7). The two molecules of nitric acid combined in the dinitrate were included in calculating nitric acid - hexamine ratios.

Immediately each reaction mixture was prepared, the flask was immersed in an ice-water bath and shaken mechanically. Reaction times were corrected empirically for the time required (one minute) for the reaction mixture to warm up to the bath temperature. The yield of RDX after any given interval was obtained by diluting the reaction mixtures tenfold with water, and allowing the diluted liquors to stand overnight to ensure complete precipitation of the RDX. The RDX was then filtered on a sintered glass crucible, washed with water, dried at 90°C . for 12 hr., and weighed. Yields were corrected for loss of RDX by solubility in the diluted liquors, and were calculated as percentage values on a total methylene basis.

(b) Results

Rates of formation and final yields of RDX were determined at 0°C . for different molar ratios of nitric acid to hexamine, at acid concentrations of 88, 91, 94, and 97%.

Maximum yield (about 40%) of RDX was obtained with all concentrations of acid down to 88%, providing the molar ratio of acid to hexamine was sufficiently high (Fig. 1). The minimum molar ratio for maximum yield was found to increase from about 26:1 with 97% acid to 110:1 with 88% acid.

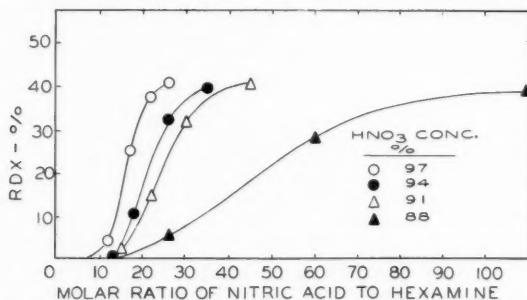


FIG. 1. Effect of nitric acid-hexamine ratio on final yield of RDX.

No induction period was observed in any of the rate curves, indicating that the rate controlling step is probably much slower than all other steps in the nitrolysis reaction. Almost identical rates of RDX formation result from the use of different concentrations of nitric acid between 88 and 97% when the molar ratio of acid - hexamine is selected so as to give the same yield in two hours at 0°C. (Fig. 2).

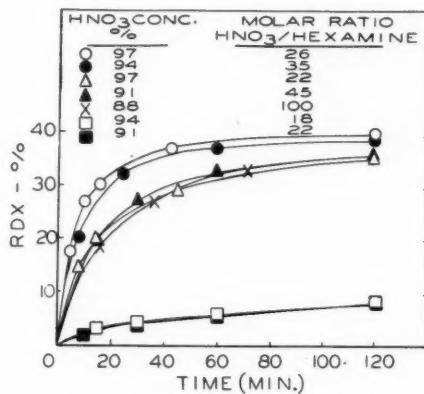


FIG. 2. Rate of RDX formation with various concentrations of nitric acid at 0°C.

Except for the first few minutes of reaction, a linear relation was found between time of reaction and $\log(a - x)$, where a is defined as a yield slightly below the values found for final yields, and x is the yield at time t . The necessity for taking a slightly below the final yield to obtain such first order lines might be due to the presence of impurities in the products of long reaction times, since these melted at 197–202°C. (corr.). For instance, Springall *et al.* have observed (15) that products from reactions at 0°C. for five and six hours were impure, melting as low as 180°C. Alternatively, slow resynthesis of hexamine fragments to yield small amounts of RDX might make the final yield values slightly high. The change in slope of the lines during the first few minutes of reaction, in the sense of a decrease in rate constant, indicates a marked change in the nitrolysis medium, and probably reflects a decrease in concentration of the agent responsible for nitrolysis, due to formation of water or other by-products of the reaction.

The initial rates of RDX formation, determined from tangents to the rate curves at zero time, were related to acid concentration and molar ratio of acid to hexamine in the manner shown in Fig. 3. The increase in initial rate with increased acid - hexamine ratio continues with molar ratios greater than the minimum required for maximum yield. An upper limit to the "initial" rate was found when yields after one minute reaction time were determined at –20°C., using 97% nitric acid (Fig. 4).

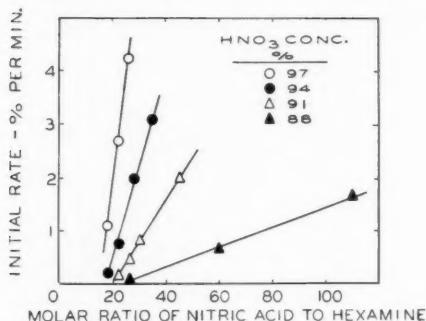


FIG. 3. Effect of nitric acid-hexamine ratio on initial rate of RDX formation at 0°C.

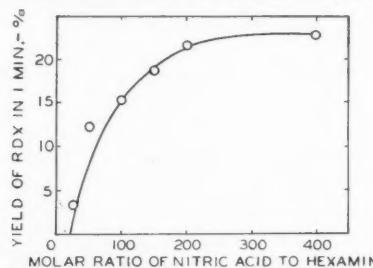


FIG. 4. Effect of nitric acid-hexamine ratio on initial rate of RDX formation with 97% nitric acid at -20°C.

When initial rates were plotted against yields after two hours, it was evident that the higher the acid concentration the higher was the initial rate necessary to attain any given yield of RDX below the maximum, i.e., the rate of RDX formation fell off more rapidly with higher acid concentrations.

The final yield of RDX calculated on a nitric acid basis (1 mole of RDX from 3 moles of nitric acid) was related to the hexamine-nitric acid molar ratio as shown in Fig. 5. For very low molar ratios of hexamine-nitric acid the

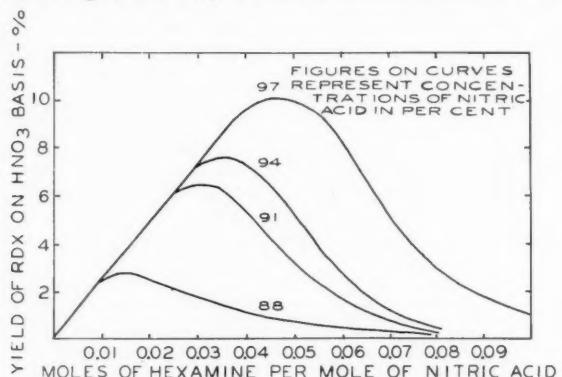


FIG. 5. Effect of hexamine-nitric acid ratio on yield of RDX on nitric acid basis.

yield of RDX is independent of acid concentration (above 88% acid) and is directly proportional to the amount of hexamine used. With increasing amounts of hexamine a point is reached where the initial rate is too small to permit maximum yields, beyond which further addition of hexamine inhibits the nitrolysis.

II. Isolation of 3, 5-Dinitrocyclotrimethylenetriamine-1-nitrate in the Direct Nitrolysis of Hexamine

When the nitrolysis of hexamine dinitrate with 97% nitric acid was allowed to proceed at -40°C., and the reaction mixture diluted with ice water after 45 sec. reaction time, a white crystalline solid was obtained, m.p. 96-98°C. (corr.) with decomposition. The method of preparation was successfully modified to use hexamine itself and 88% nitric acid, as follows:

To mechanically stirred 88% nitric acid, cooled to about -40°C., was added 30 gm. of dry hexamine during 10-15 sec. The temperature was allowed to rise to 0°C. where it was held for four to five minutes. The reaction mixture was then cooled to about -25°C. and poured over chopped ice to give a final volume of about 750 cc. When most of the ice had melted, the product was separated by suction, washed once with cold ethanol, twice with cold ether, and dried in a vacuum desiccator. Yield, approximately 22 gm., m.p. 98-99°C. (decomp.).

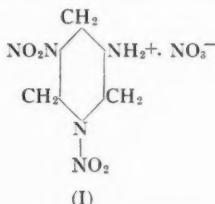
Well defined crystals of the product were obtained, and some purification effected, by dissolving it in colorless 75% nitric acid at -20°C., and slowly adding ice water with vigorous stirring, the temperature being kept at -20° to -15°C. The precipitated product was filtered, washed, and dried as before.

When the purified product was shaken with water at 0°C. and the filtrate tested with iodine - potassium iodide solution, no hexamine dinitrate tetraiodide was formed. On complete decomposition of the product in boiling water (one to two minutes), no residue of RDX remained.

Elemental analyses* of the product gave C, 15.1, 15.0; H, 3.48, 3.54; N, 34.5, 34.7. A positive diphenylamine test for nitrate ion was given by the solid, while decomposition of it in concentrated sulphuric acid, followed by ferrous sulphate titration, showed approximately one mole of nitrate ion per mole of the product. Hydrolysis of the product in water, and precipitation with nitron reagent according to the method of Cope and Barab (4) showed one mole of nitrate ion per mole, the absence of nitrite ion in the solution being demonstrated by testing with potassium iodide and starch.

On the basis of the above evidence it was concluded that the product isolated from the low temperature nitrolysis reaction was 3,5-dinitrocyclotrimethylenetriamine-1-nitrate (or 3,5-dinitro-3,5-diazapiperidinium nitrate), (I).

* We are grateful to Dr. G. F. Wright, University of Toronto, for the elemental analysis, the date of which was March 19, 1943.

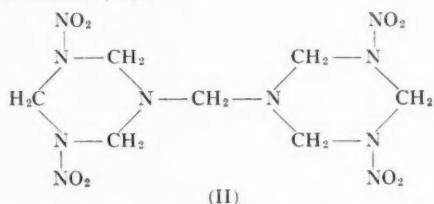


The cyclic structure of (I) has been confirmed by its conversion to 1-aceto-3,5-dinitrocyclotrimethylenetriamine (1, 3).

Freshly prepared (I), recrystallized from nitric acid, gave practically quantitative yield of RDX (mole per mole basis) when treated with 98% nitric acid in the ratio 5 moles of acid per mole of compound (I). The rate of conversion to RDX was very great, but was found to be drastically inhibited by the presence of hexamine dinitrate or its reaction products. Potassium or pyridine nitrates gave similar marked inhibition.

Conversion of (I) to RDX was also found possible by treating a suspension of it in nitromethane with boron trifluoride, and by treating a solution of it in 88% nitric acid with phosphorus pentoxide.

By treating a suspension of (I) in acetone or ethanol with dilute sodium hydroxide solution (about 0.4 mole sodium hydroxide per mole (I)), a finely divided white product was precipitated, m.p. 136°C. with decomposition. This was subsequently shown by Chute *et al.* (3) to be methylene-bis-3,5-dinitrocyclotrimethylenetriamine (II).



By dissolving (I) in pyridine and removing the pyridine nitrate and excess pyridine, a slightly yellow viscous oil, believed to be the free amine of (I), was obtained. Reaction of the oil with excess 97% nitric acid gave a good yield of RDX.

The explosive properties of (I) were examined with the kind co-operation of Canadian Industries Ltd. Its power, as determined by the ballistic mortar, was found to be approximately equal to that of RDX, whereas its impact sensitivity was slightly higher than that of RDX.

III. Kinetics of Formation of (I) and its Conversion to RDX

The amount of (I) present at any time in a hexamine dinitrate - nitric acid (85 to 91%) reaction mixture was estimated as the difference between the total

RDX producibility of the mixture and its content of unreacted hexamine dinitrate. This procedure neglects any RDX that might be derived from precursors of (I) other than hexamine dinitrate. However, such precursors would not seem to be present in appreciable amount, since 70–75% of the amount of (I) determined analytically was precipitable with ice water, which corresponded well with the amount recoverable by diluting a nitric acid solution of known content of (I) under similar conditions.

Total RDX producibility of a reaction mixture after any given time of nitrolysis was obtained by adding 98% nitric acid sufficient to obtain maximum yield of RDX in one hour at 0°C. The RDX yield was then determined by dilution, filtering, and weighing, as outlined previously.

The hexamine dinitrate content of a reaction mixture was determined by diluting it tenfold and adding *N* standard iodine solution in large excess to precipitate hexamine dinitrate tetraiodide. The tetraiodide was filtered off and the filtrate back-titrated with standard sodium thiosulphate solution. From the amount of iodine disappeared, the amount of hexamine dinitrate in the system was calculated.

In presenting the data, it is assumed that (I) was formed in theoretical yield, although the maximum yield of RDX obtained by nitrolysis of hexamine is about 40%. This assumption seems reasonable, since data to be presented later indicate that decomposition of (I) in the nitrolysis liquor is responsible for the less than theoretical yield of RDX.

Subtracting the hexamine dinitrate from the RDX producibility to obtain the amount of (I) present at any time does not take into account any conversion of (I) to RDX prior to addition of the excess 98% nitric acid. However, comparison with the rates of RDX formation determined directly showed that with the acid concentrations and amounts used, only negligible amounts of RDX were produced before addition of the excess nitric acid.

Experiments were made with 85, 88, and 91% nitric acids at different molar ratios of nitric acid to hexamine. In Fig. 6 is shown a typical pair of curves for

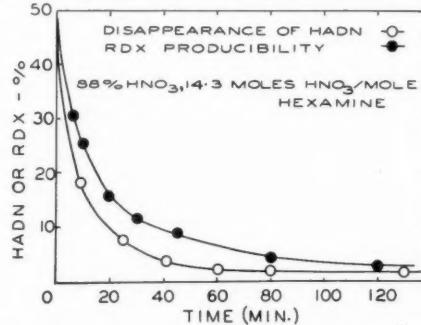


FIG. 6. Hexamine dinitrate disappearance and RDX producibility with 88% nitric acid.

disappearance of hexamine dinitrate and RDX producibility. The difference between two such curves at any time represents the amount of (I) present in the nitrolysis reaction mixture at that time.

The results obtained with 85% and 88% nitric acids are summarized in Figs. 7 and 8, respectively. A molar ratio of acid to hexamine of 10.8 was also studied using 88% acid, but the curves for RDX producibility and disappearance of hexamine dinitrate coincided, indicating that in this system no accumulation of (I) occurred. By studying the rate of decomposition of (I) added to this system, it was evident that with such a small quantity of acid it failed to accumulate because it never was formed, rather than because of rapid decomposition after formation.

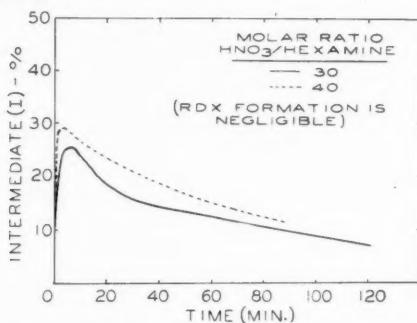


FIG. 7. Formation of intermediate (I) with 85% nitric acid.

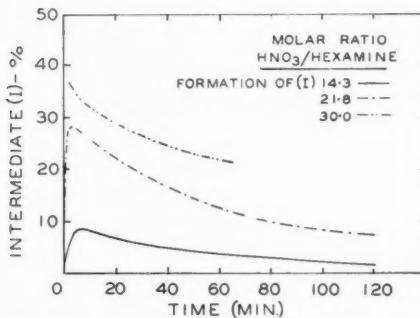


FIG. 8. Formation of intermediate (I) with 88% nitric acid.

With 91% nitric acid, at acid to hexamine molar ratios of 20 and 30, the rate of formation of (I) was so great that maxima were reached in the curves before all the hexamine dinitrate was dissolved.

It is clear from Figs. 7 and 8 that (I) is formed very rapidly during the nitrolysis of hexamine to RDX, but is unstable in the reaction medium and begins to decompose immediately. As with RDX production, higher rates of formation correspond to higher yields of (I).

The decomposition of (I) was studied in nitric acids of 80, 83, 85, and 90% concentrations, in the absence and presence of by-products of the nitrolysis reaction. The conversion of (I) to RDX was also studied, using acids of 90, 94, and 98%, and the activation energy for its conversion to RDX in 91% acid was compared with that for the conversion of hexamine to RDX in acid of the same concentration.

The rate of decomposition of (I) was determined by dissolving samples of it in the desired acid medium, shaking for various periods of time at 0°C., then converting the undecomposed (I) to RDX with excess nitric acid of 98% concentration as in previous estimations of RDX producibility. Studies of the conversion of (I) to RDX in 90, 94, and 98% acids, at 0°C., and the activation energy measurements in 91% acid were made by the earlier procedure of stopping the reaction after desired time intervals by dilution, followed by gravimetric estimation of the RDX produced. The results of the various studies may be summarized briefly, as follows.

The initial rate of decomposition of (I), estimated from tangents to the rate curves at zero time, appeared to be independent of both acid concentration and molar ratio of acid to (I) in the range 80 to 90% acid concentrations with molar ratios of acid to (I) of 18 to 30. This suggests that the reaction is first order, with a rate proportional to the amount of (I) in solution.

In "spent" liquor in which (I) had been previously decomposed in 85% nitric acid, the rate of decomposition was about 1.3 times that in 85% acid itself. The addition of (I) to the "spent" liquor from a normal hexamine nitrolysis with 98% nitric acid gave a rate of decomposition about 1.5 times the rate in pure acid of that concentration. When the initial acid concentration was reduced to 88%, however, and (I) was added after the nitrolysis reaction had proceeded for 20 min., the rate of decomposition of (I) was about three times the rate in pure 88% acid. In 85% acid to which some paraform had been added, to produce formaldehyde and nitrogen dioxide, no significant change in rate of decomposition of (I) occurred. However, addition of (I) to a solution of ammonium nitrate in 85% nitric acid (2 moles ammonium nitrate per mole (I)) gave approximately the same rate of decomposition as that obtained in the "spent" liquor from a nitrolysis reaction.

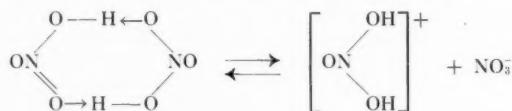
In the experiments on the conversion of (I) to RDX, perhaps the most interesting point revealed was the relatively small quantity of strong acid required for high yield of RDX. About 5 moles of 98% acid, and 8 or 9 moles of 94% acid, per mole of (I) were sufficient for essentially complete reaction.

When the rates of conversion of (I) to RDX were studied at -15, 0, and +15°C., a plot of \log (initial rate) vs. $1/T$ gave an excellent Arrhenius line from which an activation energy of 18.5 kcal. per mole was calculated. In the same way, the activation energy for the rate-controlling step in the conversion of hexamine dinitrate to RDX was evaluated as 19.1 kcal. per mole.

Discussion

The large molar ratio of nitric acid to hexamine required for maximum yield of RDX and the increase in this ratio as the concentration of acid is decreased suggests that the active nitrolyzing agent is present in the acid in relatively small amount, and that its concentration decreases with acid concentration. The behavior of the initial rate of RDX formation with variation of the acid to hexamine ratio lends support to this view.

The literature on nitric acid and nitrating agents, particularly an excellent review by Bennett, Brand, and Williams (2), indicates that a nitric acid cation, the nitracidium or nitronium ion of Hantsch (10), is responsible for many types of nitration reaction, and it is suggested that this cation, present in acids of 85-100% concentration (9), is also responsible for the nitrolysis reaction of the present study. No attempt will be made here to discuss the evidence for any particular form of the nitracidium ion, which appears to depend upon the medium (2). For present purposes it is probably preferable to regard it as $\text{NO}(\text{OH})_2^+$, formed perhaps by ionization of bimolecular nitric acid (6) as in



The apparent inhibiting effect of excess hexamine dinitrate on the rate of its nitrolysis to RDX, and the subsequent observation that other nitrates inhibited the conversion of (I) to RDX, are readily accounted for by assuming a shift of such an equilibrium to reduce the concentration of the active nitrolyzing agent, the nitracidium ion. The addition of water, or its formation during nitrolysis, would have a similar effect — nitracidium ion would lose a proton to the water molecule and revert to pseudonitric acid, $\text{NO}_2\cdot\text{OH}$.

The influence of hexamine-nitric acid ratio on the yield of RDX may also be explained by assuming a relatively small concentration of active nitrolyzing agent in the nitrolysis mixtures. The higher initial rate necessary to attain given yield with acids of higher concentrations may be ascribed to a greater inhibiting effect of water and other by-products on the nitracidium ion concentration when smaller molar ratios of acids are used. Similarly, the maximal yields on a nitric acid basis (Fig. 5) indicate that beyond a certain concentration of hexamine in given amount of acid, the rate of RDX formation is so reduced that decrease of yield results. This optimal concentration of hexamine might be expected to be higher the more concentrated the acid, i.e., the greater the amount of nitracidium ion present, and this is the behavior observed.

If nitracidium ion, derived from associated nitric acid molecules, is the active nitrolyzing agent, the initial rate of formation of RDX should be proportional to the concentration of nitracidium ion in the reaction system, i.e., proportional

to the concentration of associated nitric acid molecules. In Fig. 9 is plotted the change in intensity of the 1.017μ infrared absorption band with nitric acid concentration as determined by Dalmon and Freymann (6), who attributed this band to associated acid molecules. In the same figure is plotted a series of values showing the change in initial rate of RDX formation at 0°C . with variation in initial acid concentration, for a 40 to 1 molar ratio of nitric acid to hexamine. The correspondence between the curves would seem to provide strong supporting evidence for nitracidium ion as the nitrolyzing agent in the rate controlling step of RDX formation from hexamine. The correspondence is less favorable at lower acid to hexamine molar ratios, which is to be expected if hexamine dinitrate or its initial reaction products (possibly including water) decrease the nitracidium ion concentration.

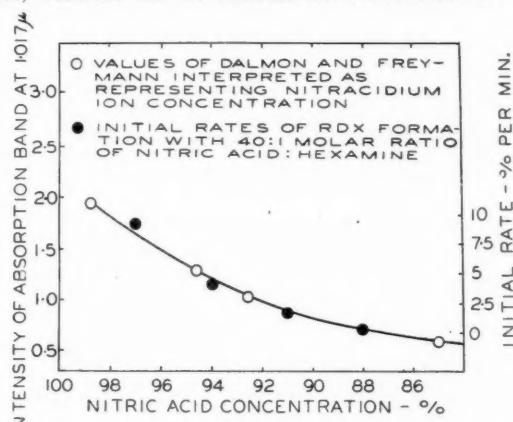


FIG. 9. Comparison of nitracidium ion concentration with initial rate for various nitric acid concentrations.

A more satisfactory comparison of the initial rate of RDX formation with the nitracidium ion concentration inferred from the results of Dalmon and Freymann is obtained by plotting the slopes of the lines in Fig. 3 against the intensity of the absorption band at 1.017μ . This is shown in Fig. 10, which is interpreted as rather convincing evidence in support of the view that nitracidium ion is the nitrolyzing agent in the formation of RDX.

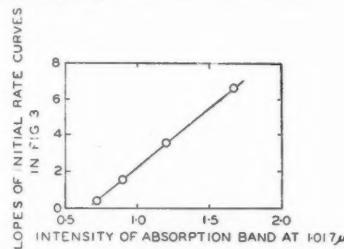


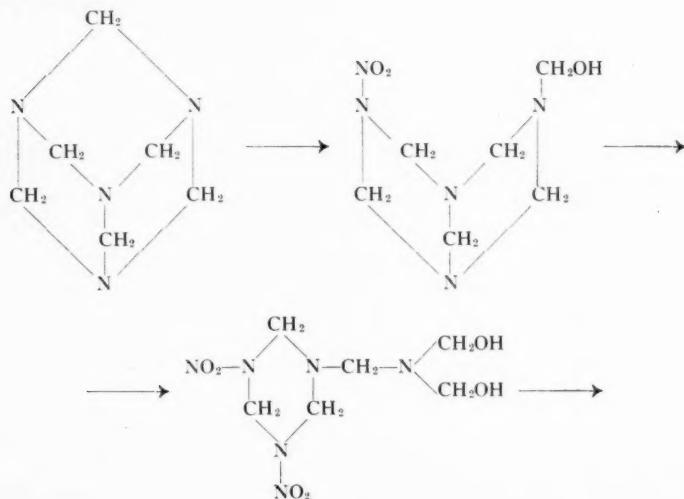
FIG. 10. Change in initial rate as a function of nitracidium ion concentration.

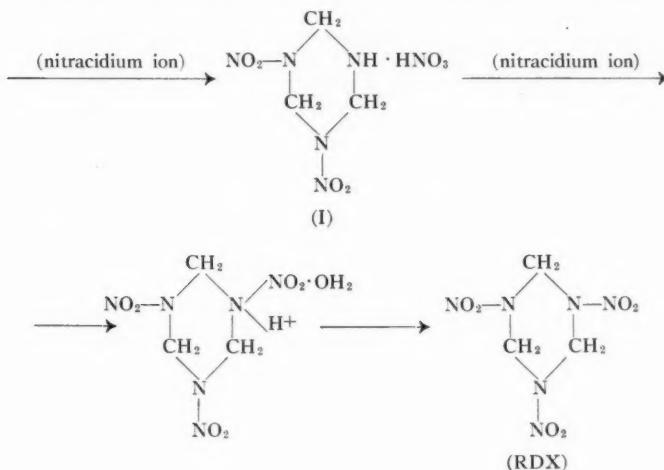
If the nature of the nitrolyzing agent may be regarded as reasonably established, there still remains the problem of determining the sequence of steps by which the hexamine molecule is converted to RDX. In the absence of evidence by which to establish the mechanism completely it is proposed to outline only the simplest scheme by which the kinetic results might be satisfactorily explained.

The very rapid disappearance of hexamine dinitrate in reaction mixtures capable of producing maximum yields of RDX, together with the isolation and behavior of (I), indicate that the final conversion of (I) to RDX is the rate controlling step in the direct nitrolysis of hexamine to RDX. This conversion appears to be retarded by by-products of the reaction, and to be in competition with decomposition of (I) to water-soluble products, such that unless (I) is converted to RDX within approximately two hours, low yields of RDX result. (Low yields of RDX cannot be due to its decomposition by nitracidium ion, since no decrease in yield was observed when reaction mixtures were allowed to remain undiluted for long periods.)

The fact that the activation energy for the conversion of (I) to RDX is, within experimental error, the same as the activation energy for the conversion of hexamine dinitrate to RDX provides reasonable grounds for assuming that (I) is a true intermediate in the over-all reaction, and substantiates the conclusion that the conversion of (I) to RDX is the rate-controlling step. On this basis, it further appears that the conversion of hexamine to RDX involves only limited degradation of the hexamine molecule.

The simplest sequence of reactions which would seem to be in accord with the several experimental observations and deductions from the kinetic data is probably as follows:





Although methylol groups are indicated in the above scheme it should be understood that they may be esterified at the time of nitrolysis or subsequently. It is probable that esterification of such groups occurs rapidly, since there are indications that water is formed early in the nitrolysis reaction.

The probable existence of hexamine as the dinitrate salt in nitric acid has not been indicated in the equations, since there is no reason to believe that the combined nitric acid molecules have any bearing on the mode of rupture of the hexamine molecule.

As mentioned earlier, there are some indications from the present study that fragments derived from the hexamine molecule may undergo a resynthesis, perhaps to hexamine, with further ultimate production of RDX.

It should be emphasized that the scheme suggested above merely represents a simple but adequate interpretation of the information available from kinetic studies. Further study may reveal that the mechanism is more complex, but in the absence of concrete evidence to the contrary, it seems reasonable to take the simplest interpretation as a working basis.

Acknowledgment

Grateful acknowledgment is made to the Committee on Research, McGill University, for financial assistance in the preparation of this manuscript.

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STUDIES ON RDX AND RELATED COMPOUNDS

II. THE NITROLYSIS OF HEXAMINE IN ACETIC ACID¹

BY M. KIRSCH² AND C. A. WINKLER

Abstract

Acetic acid has a harmful effect on the reaction rate and on the yield of RDX at 1°C. and at 30°C. for a given nitric acid - hexamine ratio below a certain optimum value. At the optimum, however, the maximum yield of 80% is obtained at both temperatures. The deleterious effect of acetic acid may be explained by assuming that the concentration of the active nitrolyzing agent (nitracidium ion) is decreased by reaction between acetic acid and nitric acid.

Introduction

The nitrolysis reaction between hexamethylene tetramine (hexamine) and fuming nitric acid to produce *cyclo*-trimethylenetrinitramine (RDX) may be formulated as:



but much more nitric acid is required than is indicated stoichiometrically. Vroom and Winkler (1) found that at 0°C. the maximum yield of RDX was obtained only if the molar ratio of 97% nitric acid: hexamine was at least 26: 1. With decreasing concentration of nitric acid to 88%, the amount of acid necessary to produce the maximum yield of RDX increased progressively.

No kinetic data on the nitrolysis of hexamine in the presence of solvents are available and the present study was made to determine whether the characteristics of the nitrolysis reaction were fundamentally altered by the presence of a solvent.

Experimental

Stock solutions of hexamine of desired compositions were prepared in glacial acetic acid. The amount of water in these solutions, determined in the Karl Fischer reagent, was found to be insignificant. The amount of hexamine was determined from time to time by titration with a solution of sulphuric acid in acetic acid. During the titration, hexamine disulphate was precipitated. The end point was detected with an acetic acid solution of methyl violet which changed from violet to green. In this way it was found that no deterioration of the stock solutions occurred.

In making an experiment, the appropriate volume of hexamine solution was pipetted into a measured volume of solid 97% nitric acid, contained in a 250 ml. Erlenmeyer flask, cooled in an acetone - dry ice bath. The length of time

¹ Manuscript received in original form December 17, 1948, and, as revised, August 28, 1950.
Contribution from the Physical Chemistry Laboratory, McGill University, Montreal, Que., with financial assistance from the National Research Council of Canada.

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required for the addition of the hexamine varied with the solution, depending on its viscosity, but it never exceeded two minutes. Since the temperature did not rise above -25°C . during the addition, there was no appreciable reaction (1). The flask was then shaken in a thermostat at 1°C . or 30°C ., the initial time being taken as one minute after placing the flask in the thermostat, since it required approximately this time for the reaction mixture to attain the thermostat temperature. After shaking for a definite time, the reaction was quenched by diluting with water to about 200 ml. The mixture was allowed to stand overnight at room temperature to ensure complete precipitation of the RDX. The solid was filtered into tared sintered glass crucibles, dried at $100\text{--}110^{\circ}\text{C}$. for four hours and weighed.

Final yields were obtained by allowing the reaction to proceed for a week at 1°C . and for 24 hr. at 30°C . No further increases in yield were observed after these times.

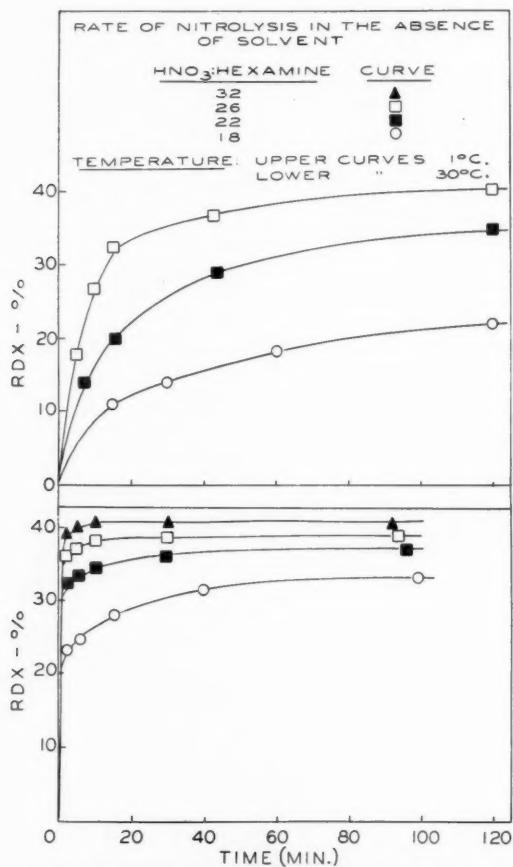


FIG. 1. Rate of nitrolysis in the absence of solvent.

The solubility of RDX in the diluted liquors was found to be negligible in all the experiments.

Solid (presumably hexamine dinitrate) precipitated as soon as the hexamine solution was added to the nitric acid, but dissolved as the mixture warmed up to reaction temperature.

Yields are calculated on the assumption that one mole of hexamine should yield two moles of RDX.

Results and Discussion

Experiments were made at both 1°C. and at 30°C. using molar ratios of acetic acid - hexamine between 4.3:1 and 10.5:1 and varying the nitric acid - hexamine ratio between 81:1 and 26:1.

When no solvent was present, the rate curves of Fig. 1 were obtained, while typical results with acetic acid present are given in Fig. 2.

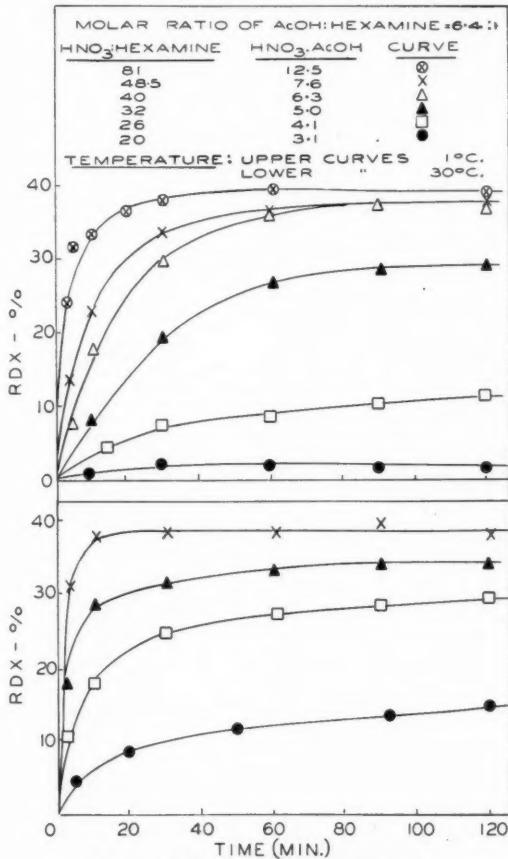


FIG. 2. Rate of nitrolysis in acetic acid.

A comparison of the curves in Fig. 1 with those in Fig. 2 and with the data given by Vroom and Winkler (1) shows that acetic acid may have a harmful effect on both the rate of nitrolysis and on the final yield of RDX for a given molar ratio of nitric acid to hexamine. This is more clearly shown in Fig. 3. It is evident that if the molar ratio of nitric acid to hexamine is increased sufficiently in the presence of solvent, the maximum yield of approximately 40% is approached regardless of temperature.

Effect of Acetic Acid on the Nitrolysis of Hexamine

Fig. 3 shows that even with the most dilute solution of hexamine in acetic acid (molar ratio, 10.5:1) the final yield of RDX approaches the maximum of 40% at a molar ratio of nitric acid to hexamine of about 48:1. In the absence of solvent this yield is obtained when the molar ratio is only 26:1. It appears, therefore, that acetic acid has reacted with some of the nitric acid and made it unavailable for nitrolysis.

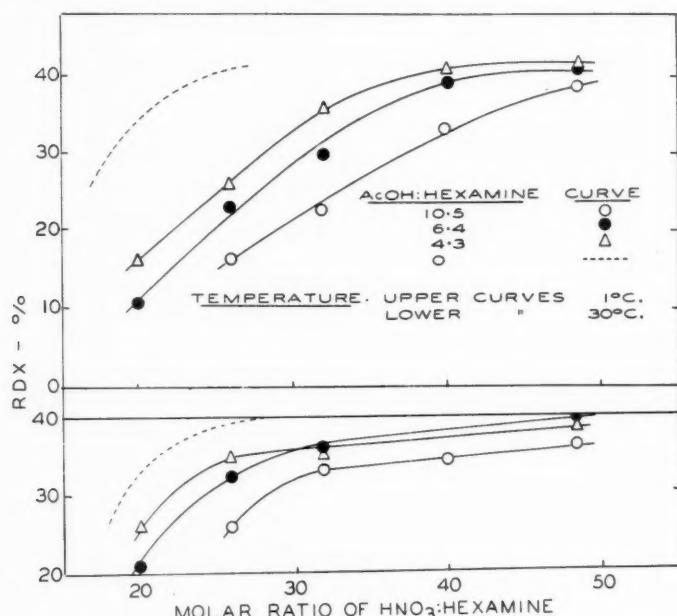


FIG. 3. *Effect of nitric acid - hexamine ratio on final yield in acetic acid.*

The effective nitrolyzing agent has been assumed to be nitracidium ion (1), produced according to the equilibrium equation:



If acetic acid acts as a base toward nitric acid such that



the first equilibrium would be shifted to the left because of the decrease in nitric acid concentration and increase in nitrate ion concentration occasioned by the second equilibrium.

On this basis it is possible to explain qualitatively the results obtained with acetic acid. For a given nitric acid - hexamine ratio, the nitracidium ion concentration should decrease with increasing acetic acid concentration, and, therefore, the rate of production of RDX should also decrease. This is the behavior observed in the presence of acetic acid. Further, if the equilibrium constant for Reaction (2) is greater than for Reaction (1), increasing the nitric acid concentration should increase the concentration of nitracidium ion and, hence, the rate of reaction.

The effect of increased temperature is to decrease the harmful effect of the solvent. This is the behavior that would be expected if the equilibrium constant for Reaction (2) does not increase so rapidly with increasing temperature as does that of Reaction (1).

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SYNTHESIS, POTENTIOMETRIC TITRATIONS, AND ULTRA-VIOLET ABSORPTION SPECTRA OF 3-OXO-2-PHENYL-4,4-DISUBSTITUTED-5-PYRAZOLONES AND 3-HYDROXY-2-PHENYL-4-MONOSUBSTITUTED-5-PYRAZOLONES¹

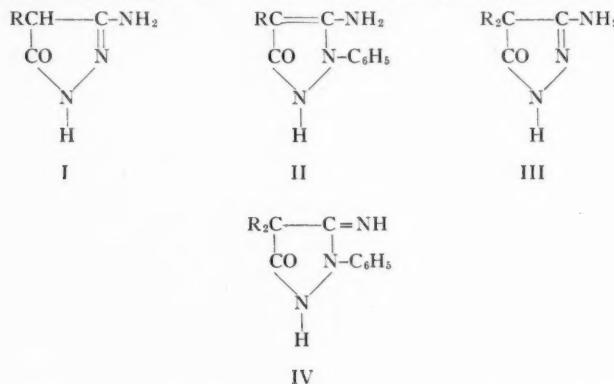
BY PAUL E. GAGNON, JEAN L. BOIVIN,² AND PAUL A. BOIVIN³

Abstract

A number of 3-oxo-2-phenyl-4,4-disubstituted-5-pyrazolones and 3-hydroxy-2-phenyl-4-monosubstituted-5-pyrazolones have been prepared by reacting ethyl di- and monosubstituted malonates with phenylhydrazine in the presence of sodium ethylate. The evidence of an oxo group in position 3 in the disubstituted pyrazolones has been obtained by hydrolyzing 4,4-dibenzyl-3-imino-2-phenyl-5-pyrazolone and identifying the product of the reaction with 4,4-dibenzyl-3-oxo-2-phenyl-5-pyrazolone prepared from dibenzylmalonic ester and phenylhydrazine. A study of the ultraviolet absorption spectra of the pyrazolones has been made and their ionization constants have been determined by potentiometric titrations.

Introduction

The condensation products of ethyl mono- and disubstituted cyanoacetates with hydrazine and hydrazine derivatives in the presence of an alkaline catalyst have been reported in previous papers (2, 3, 6). They consist of four types of pyrazolones: 4-monosubstituted-3-amino-5-pyrazolones (I), 4-monosubstituted-3-amino-2-phenyl-5-pyrazolones (II), 4,4-disubstituted-3-amino-5-pyrazolones (III), and 4,4-disubstituted-3-imino-2-phenyl-5-pyrazolones (IV).



It is well known that these pyrazolones may have several structures due to prototropic shifts. Tautomeric forms may arise from the displacement of one hydrogen atom of the amino group in position 3 of compounds I, II, and III

¹ Manuscript received July 3, 1950.

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to either position 2 or 4, yielding a 3-imino derivative as is the case of pyrazolone IV. These structures have been assigned to these substances because of their chemical properties and their behavior toward alkalies and acids (2).

Since all these pyrazolones were prepared in the presence of an alkaline catalyst, in some cases 33% sodium hydroxide, they were thought to be stable toward alkalies. However, in attempts to transform a potential imino group in position 3 into an oxo group, it has been found that pyrazolones of types I, II, and III were stable in the presence of aqueous alkalies while compounds of type IV were unstable. After refluxing pyrazolones I, II, and III ($R: C_6H_5CH_2$) for 15 hr. in aqueous sodium hydroxide, they were recovered unchanged, whereas the same treatment of 4,4-dibenzyl-3-imino-2-phenyl-5-pyrazolone (IV, $R: C_6H_5CH_2$) yielded ammonia and a new compound which was soluble in alkalies and insoluble in acids. The elemental analysis corresponded to the formula of 4,4-dibenzyl-3-oxo-2-phenyl-5-pyrazolone (V, $R: C_6H_5CH_2$).

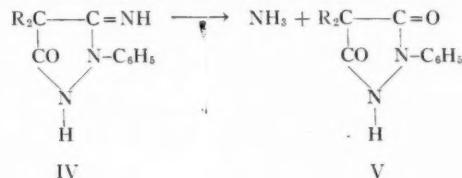


TABLE I
PROPERTIES OF 4,4-R₂-3-OXO-2-PHENYL-5-PYRAZOLONES (V)

R	Formula	M.p., °C.	Analysis, %		Ultraviolet absorption maxima			
			Nitrogen		Neutral		Alkaline	
			Calc.	Found	Å	Log E _m	Å	Log E _m
CH ₃ *	C ₁₁ H ₁₂ O ₂ N ₂	179-180	13.7	13.4	2380 2730	4.04 3.77	2430 2920	4.17 3.74
C ₂ H ₅	C ₁₃ H ₁₆ O ₂ N ₂	110-111	12.1	12.1	2400 2730	4.24 4.01	2500 2800	4.21 3.97
C ₃ H ₇	C ₁₅ H ₂₀ O ₂ N ₂	105-106	10.8	10.7	2400 2730	4.13 3.91	2520 2800	4.13 4.05
C ₅ H ₁₁	C ₁₉ H ₂₈ O ₂ N ₂	211-213	8.86	8.82	2340 2800	4.39 3.47	2480 2800	3.97 3.87
C ₇ H ₁₅	C ₂₃ H ₃₆ O ₂ N ₂	136-137	7.53	7.50	2360 2800	4.08 3.41	2360 2800	3.97 3.47
C ₆ H ₅ CH ₂	C ₂₃ H ₂₆ O ₂ N ₂ †	258-259	7.86	7.85	2420 2780	3.96 3.62	2500 2950	3.91 3.59
C ₆ H ₅ CH ₂ ‡	C ₂₃ H ₂₆ O ₂ N ₂	258-259	7.86	7.85	2420 2780	3.94 3.60	2500 2950	3.90 3.54

*Ref. 6. †Calc. C, 77.5%; H, 5.62%. Found: C, 77.1%; H, 5.70%.

‡By hydrolysis of IV into V.

It was thought possible to synthesize compound V from disubstituted malonic esters and phenylhydrazine. A survey of the literature revealed that only two members of this series of compounds have been prepared by Conrad and Zart (1), mainly the diethyl and the dipropyl derivatives (V, R: C₂H₅ and C₃H₇). It was then of interest to extend this series of pyrazolones made from disubstituted malonates and phenylhydrazine in the presence of sodium ethylate.

Table I lists some of these compounds together with their physical properties and spectrophotometric data.

Compound V (R: C₆H₅CH₂) obtained by the alkaline hydrolysis of the 3-imino derivative was shown by a mixed melting point determination to be identical with the pyrazolone synthesized by the method described above. Another proof of identity of the two pyrazolones was obtained from the ultraviolet absorption determinations. The spectra in neutral and alkaline solutions were identical (Fig. 1).

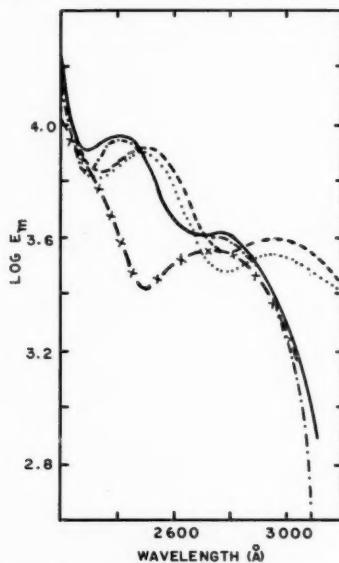
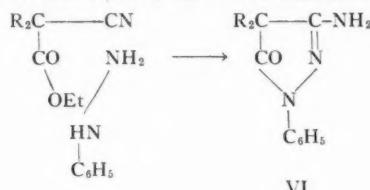


FIG. 1. Ultraviolet absorption spectra.
 — 4,4-Dibenzyl-3-oxo-2-phenyl-5-pyrazolone (Ethanol)
 - - - Ditto (0.01*N* sodium hydroxide in ethanol)
 - · - - Ditto (By hydrolysis of IV) (Ethanol)
 · · · · Ditto " " " (0.01*N* sodium hydroxide in ethanol)
 -x-x-x- 4,4-Dibenzyl-3-imino-2-phenyl-5-pyrazolone (Ethanol)

It may be also emphasized that this hydrolysis of a 3-iminopyrazolone into a 3-oxopyrazolone may be considered as a proof of the position of the phenyl group of compounds of type IV. If it is assumed that a disubstituted cyanoacetic ester reacts with phenylhydrazine to give 1-phenylpyrazolone (VI) as

cyanooacetic ester does (6), the reaction would lead to a 3-aminopyrazolone of general formula II. Moreover, structure VI would be that of a compound in-



soluble in alkalies and soluble in active acids, whereas the 2-phenylpyrazolones (IV) are soluble in alkalies and insoluble in acids. In addition to these different properties, compounds of type VI could not be hydrolyzed to a 3-oxo-1-phenylpyrazolone (V). Hence, it is reasonable to state that a disubstituted cyanooacetic ester reacts with phenylhydrazine in the presence of sodium ethylate to yield IV instead of VI.

In addition to these 4,4-disubstituted-3-oxo-2-phenyl-5-pyrazolones, a number of 4-monosubstituted-3-hydroxy-2-phenyl-5-pyrazolones (VII) have been synthesized by a similar method, starting from monosubstituted malonic esters and phenylhydrazine. Table II shows their properties together with their spectrophotometric data.

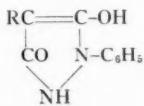
TABLE II
PROPERTIES OF 4-R-3-HYDROXY-2-PHENYL-5-PYRAZOLONES (V)

R	Formula	M.p., °C.	Analysis, %		Ultraviolet absorption maxima			
			Nitrogen		Neutral		Alkaline	
			Calc.	Found	Å	Log E_m	Å	Log E_m
H*	C ₉ H ₈ O ₂ N ₂	191-192	15.9	15.9	2400 2700	4.08 3.83	2470 2800	4.02 3.8 ⁱ
CH ₃	C ₁₀ H ₁₀ O ₂ N ₂	177-178	14.7	14.6	2400 2700	4.04 3.84	2520 2780	4.03 4.03
C ₂ H ₅ †	C ₁₁ H ₁₂ O ₂ N ₂	106-107	13.7	13.8	2410 2740	4.05 3.85	2700 2800	4.03 3.90
C ₃ H ₇	C ₁₂ H ₁₄ O ₂ N ₂	186-187	12.8	12.9	2400 2760	4.11 3.61	2500 2850	4.11 3.63
C ₄ H ₉	C ₁₃ H ₁₆ O ₂ N ₂	149-150	12.1	12.0	2400 2720	4.11 3.61	2400 2850	3.74 3.16
C ₅ H ₁₁	C ₁₄ H ₁₈ O ₂ N ₂	139-140	11.4	11.2	2720	3.95	2400 2840	3.74 3.19
C ₈ H ₁₇	C ₁₇ H ₂₄ O ₂ N ₂	154-155	9.72	9.73	2380 2800	4.06 3.23	2380 2780	3.80 3.41
C ₆ H ₅ CH ₂	C ₁₆ H ₁₄ O ₂ N ₂	188-189	10.5	10.2	2540 2750	4.07 4.08	2550 2750	4.12 4.16

*Ref. 1.

†Ref. 5.

ⁱ Inflection point.



VII

The 4,4-disubstituted-3-oxo-2-phenyl-5-pyrazolones gave, in most cases, in neutral solution spectra exhibiting two maxima, one at 2400 Å and the other at about 2800 Å (Table I). In alkaline solution, the curves are similar in shape but are bathochromically displaced by about 100 Å. Fig. 2 shows the spectra of 4,4-diethyl-3-oxo-2-phenyl-5-pyrazolone and of the 4,4-dibenzyl derivative obtained by hydrolysis of the parent 3-iminopyrazolone. In the case of 4,4-dibenzyl-3-imino-2-phenyl-5-pyrazolone (Fig. 1), it can be seen that the presence of an imino group in position 3 broadens the absorption band at 2800 Å, while its replacement by an oxo group gives a spectrum similar to that of the 4,4-diethyl-3-oxo-2-phenyl-5-pyrazolone.

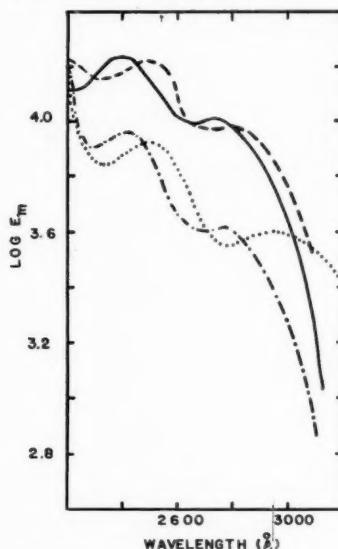


FIG. 2. Ultraviolet absorption spectra.
 — 4,4-Diethyl-3-oxo-2-phenyl-5-pyrazolone (Ethanol)
 - - - Ditto (0.01*N* sodium hydroxide in ethanol)
 - · - 4,4-Dibenzyl-3-oxo-2-phenyl-5-pyrazolone (Ethanol)
 Ditto (0.01*N* sodium hydroxide in ethanol)

The 4,4-disubstituted-3-oxo-2-phenyl-5-pyrazolones and their monosubstituted derivatives show similar spectra in neutral and alkaline solutions (Fig. 3 and Table II), except that the maximum lying at 2400 Å has been shifted hypsochromically by some 40 Å. It is evident that the presence of a substituent in position 4 has little influence on the absorption spectra of these compounds, if we compare 3-hydroxy-2-phenyl-5-pyrazolone with 4-ethyl-3-hydroxy-2-phenyl-5-pyrazolone.

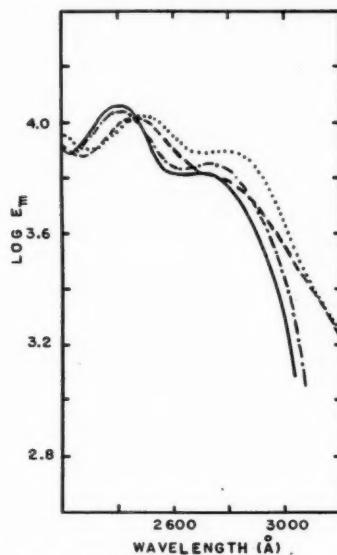


FIG. 3. Ultraviolet absorption spectra.
 — 3-Hydroxy-2-phenyl-5-pyrazolone (Ethanol)
 - - - Ditto (0.01N sodium hydroxide in ethanol)
 - · - 4-Ethyl-3-hydroxy-2-phenyl-5-pyrazolone (Ethanol)
 Ditto (0.01N sodium hydroxide in ethanol)

Potentiometric Titrations

Since all the pyrazolones of types I, II, III, IV, V, and VII were slightly soluble or insoluble in water, they were dissolved in an alkaline solution containing a known amount of alkali and titrated with a standard acid while the pH values were recorded with a Beckman pH meter, Model H2. The results are given in Table III and shown graphically in Figs. 4 and 5.

TABLE III
POTENTIOMETRIC TITRATIONS OF PYRAZOLONES

Compounds	R	Amount of substance, moles $\times 10^4$	Approx. amount of sodium hydroxide used, moles $\times 10^4$	$pK_a \dagger$
VII	H	6.44*	6.2	4.8
VII	C ₆ H ₅ CH ₂	5.91	6.0	4.7
V	"	4.55	5	8.2
I	"	9.64	10	8.7
II	"	4.70	5	7.6
III	"	4.53	4	10.4
IV	"	2.75	3	10.6
H H C ₆ H ₅ CON-NCOC ₆ H ₅		9.84	10	9.0

*These pyrazolones were dissolved in 25 ml. of 0.101N sodium hydroxide and titrated with 0.106N hydrochloric acid.

†As determined from the curves.

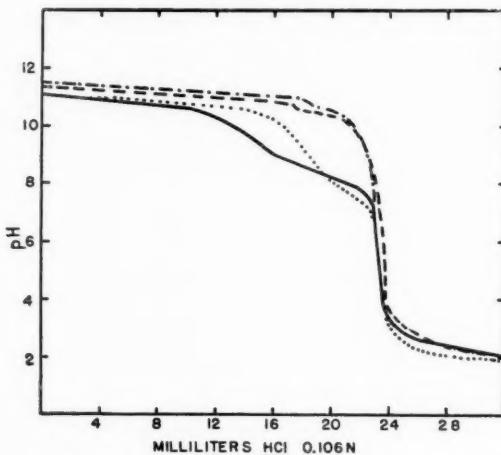


FIG. 4. Titration curves.

— 4-Benzyl-3-amino-5-pyrazolone
 4-Benzyl-3-amino-2-phenyl-5-pyrazolone
 - - - 4,4-Dibenzyl-3-amino-5-pyrazolone
 - · - 4,4-Dibenzyl-3-imino-2-phenyl-5-pyrazolone

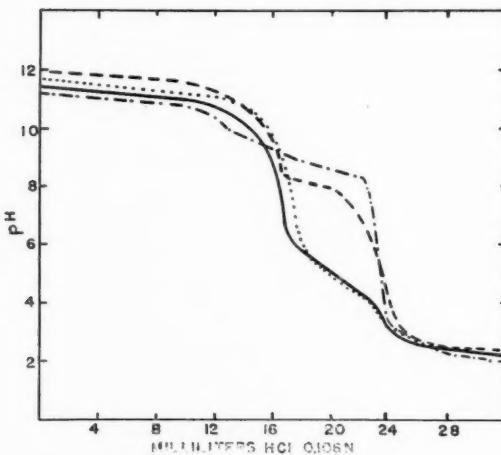


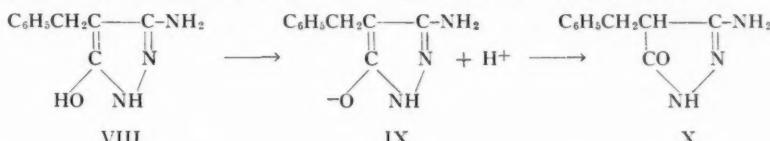
FIG. 5. Titration curves.

— β -Hydroxy-2-phenyl-5-pyrazolone
 4-Benzyl- β -hydroxy-2-phenyl-5-pyrazolone
 - - - 4,4-Dibenzyl- β -oxo-2-phenyl-5-pyrazolone
 - · - *N,N'*-Dibenzoylhydrazine

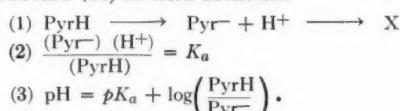
All the titration curves obtained have the same shape. At high pH values, the acid is used to neutralize the excess of alkali required to dissolve the pyrazolones, and there is a break in the curve which is more or less pronounced according to the compound used. A flat portion appears which is

due to the neutralization of the substance present. It is apparent from the curve that all these compounds are monobasic acids of different activity (Table III).

The actual solutions titrated may be considered as buffer solutions. If it is assumed that 4-benzyl-3-amino-5-pyrazolone has formula VIII, this compound may dissociate in water into the pyrazolone ion (IX) and (H^+).



Since this ion (Pyr^-) is a radical of a slightly active acid (Fig. 4), it will combine with water to form the compound itself (PyrH) which by prototropic shift will revert to its keto structure (X) in acid solution.



Hence the ionization constant expressed as pK_a value would be given by Equation (3) when half the sodium salt of the pyrazolone would be dissociated or in the present case half-neutralized with acid. This implies

$$\log \frac{\text{PyrH}}{\text{Pyr}^-} = 0.$$

The pH value of the midpoint of the flat portion of the curve will give the ionization constant of the pyrazolones with a good approximation.

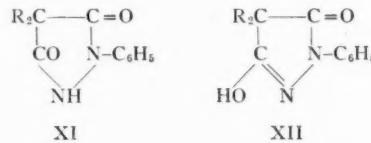
Therefore, it can be seen that 4-benzyl-3-amino-5-pyrazolone (I) has a pK_a value of 8.7 (Fig. 4), whereas that of the corresponding 2-phenylpyrazolone (II) is 7.6; 4,4-dibenzyl-3-amino-5-pyrazolone (III) and the corresponding 2-phenyl- derivative (IV) show a lower activity and have a pK_a value of 10.4 and 10.6 respectively. Moreover, their tendency to form sodium salt was very weak, whereas compounds of types I and II dissolved readily in a sodium hydroxide solution. It must be emphasized that these compounds are less acidic in character than carbon dioxide. For this reason they are precipitated readily from their alkaline solution by means of carbon dioxide.

If a comparison is made between the 3-amino and iminopyrazolones (I, II, III, IV) and the 3-oxo and hydroxypyrazolones (V, VII), it is noted that the latter are more acidic than the former. 3-Hydroxy-2-phenyl-5-pyrazolone (VII, R: H) and 4-benzyl-3-hydroxy-2-phenyl-5-pyrazolone (VII) have pK_a values of 4.8 and 4.7 respectively, indicating that they are monobasic acids of about the same strength. Moreover, the 4,4-disubstituted 3-oxo-2-phenyl-5-pyrazolone (V) has a markedly decreased acidity, since its pK_a value is 8.2. From these data, it is evident that a mixture of these 4-mono and 4,4-disubsti-

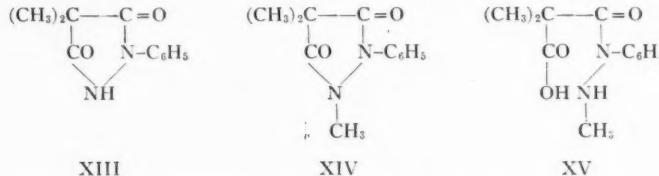
tuted pyrazolones in alkaline solution can be separated by means of carbon dioxide. The 4,4-disubstituted derivative will be precipitated whereas the 4-monosubstituted pyrazolone will remain in solution and can be precipitated by acetic acid.

Structure of 4,4-Disubstituted-3-oxo-2-phenyl-5-pyrazolones

These 4,4-disubstituted pyrazolones may have two tautomeric structures (XI and XII).



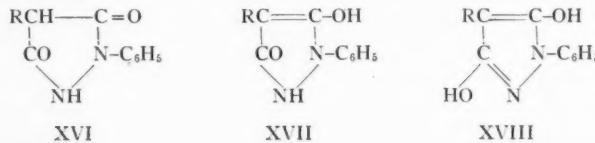
From the work of Michaelis and Schenck (4, 5) there is evidence that these compounds are best represented with an oxo group in position 3 whereas a hydroxy or oxo group may be present in position 5. The methylation of 4,4-dimethyl-3-oxo-2-phenyl-5-pyrazolone (XIII) yields 1,4,4-trimethyl-3-oxo-2-phenyl-5-pyrazolone (XIV) which, on hydrolysis in alkaline solution, gives compound XV.

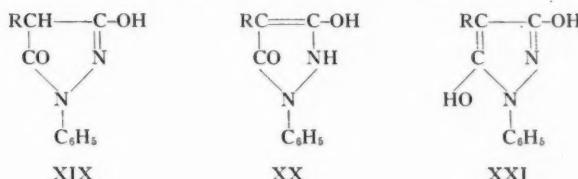


Since these 4,4-disubstituted-3-oxo-2-phenyl-5-pyrazolones have a pK_a value comparable to that of N,N'-dibenzoylhydrazine (Fig. 5) and gave a negative ferric chloride test, they should have in neutral and acid solutions a keto group in position 5, the lactam form XI. However, in alkaline solution the lactim form XII is likely to be present. These structures would be in agreement with the ultraviolet absorption spectra of these compounds which exhibit, in alkaline solution, a band lying in the absorption region of the keto group.

Structure of 4-Monosubstituted-3-hydroxy-2-phenyl-5-pyrazolones

Several tautomeric structures are possible in the case of 4-monosubstituted-3-hydroxyphenylpyrazolones and only six will be considered (XVI-XXI).





Since these pyrazolones are monobasic acids giving a positive color test with ferric chloride, only structures of types XVII, XIX, and XX are left for consideration. Moreover, if the partial phenolic structure is represented by $-C=C-OH$, as it is the case for several compounds, XIX should be rejected. From the chemical properties and ultraviolet absorption spectra of these pyrazolones, structures XVII and XX seem to be the best ones.

Experimental*

4,4-Disubstituted-3-oxo-2-phenyl-5-pyrazolones (V)

To a cold solution of sodium (0.3 mole) in absolute ethanol (200 ml.) were added ethyl disubstituted malonate (0.1 mole) and phenylhydrazine hydrochloride (0.1 mole). The mixture was heated at about 160°C. in an oil bath for 15 hr. The suspension which contained precipitated sodium salt was evaporated to dryness under reduced pressure. The residue was dissolved in water (100 ml.) and the solution extracted with ether to remove unchanged reagents. The aqueous layer was saturated with carbon dioxide when the pyrazolone precipitated as a crystalline product.

The 4,4-disubstituted pyrazolones obtained by this method were recrystallized from ethanol. They were all soluble in alkalies and ether, and insoluble in sodium carbonate solution. The ferric chloride test was negative. The yields varied 50 to 60%. The properties are summarized in Table I.

4-Monosubstituted-3-hydroxy-2-phenyl-5-pyrazolones (VII)

These substances were prepared by the same method as described above for 4,4-disubstituted-3-oxo-2-phenyl-5-pyrazolones, except that after the crude alkaline solution of these compounds had been extracted with ether, the aqueous layer was saturated with carbon dioxide and filtered from impurities. The filtrate was then treated with an excess of acetic acid (50%) until precipitation was complete. These pyrazolones were usually recrystallized from water. They were isolated in yields varying from 60 to 80%, and the properties are given in Table II.

All these compounds were soluble in alkalies, water, ethanol, ether, and sodium carbonate. They give a positive ferric chloride test indicating their phenolic character.

*All melting points were uncorrected.

4,4-Dibenzyl-3-oxo-2-phenyl-5-pyrazolones (V, R: C₆H₅CH₂)

A solution of 4,4-dibenzyl-3-imino-2-phenyl-5-pyrazolone (2) (3 gm.) in aqueous sodium hydroxide (5%, 100 ml.) was refluxed for 15 hr. during which time ammonia was evolved. The solution was evaporated to dryness and the residue treated in the usual way. A compound, melting at 258–259°C. was obtained. Yield, 2.8 gm. (97%).

By determination of mixed melting point and ultraviolet absorption spectra (Fig. 1), this compound was found to be identical with the substance already prepared (V, R: C₆H₅CH₂).

When 4-benzyl-3-amino-5-pyrazolone (I, R: C₆H₅CH₂), 4-benzyl-3-amino-2-phenyl-5-pyrazolone (II, R: C₆H₅CH₂), and 4,4-dibenzyl-3-amino-5-pyrazolone (III, R: C₆H₅CH₂) were treated in the same way, the starting materials were recovered unchanged, indicating that these compounds have no imino group in position 3 due to tautomeric changed in the molecule.

Separation of 4-Monosubstituted-3-hydroxy-2-phenyl-5-pyrazolones (VII) and 4,4-Disubstituted-3-oxo-2-phenyl-5-pyrazolones (V)

4-Benzyl-3-hydroxy-2-phenyl-5-pyrazolone (1 gm.) and 4,4-dibenzyl-3-oxo-2-phenyl-5-pyrazolone (1 gm.) were dissolved in a solution of sodium hydroxide (5%, 50 ml.) and saturated with carbon dioxide. A compound separated out which was filtered and recrystallized from ethanol, m.p. 258–259°C. Yield, 0.95 gm. This pyrazolone was the disubstituted derivative. The filtrate was treated with an excess of acetic acid. Carbon dioxide was evolved and a precipitate was formed. It was filtered and recrystallized from ethanol, m.p. 188–189°C. Yield, 0.89 gm. This compound was 4-benzyl-3-hydroxy-2-phenyl-5-pyrazolone.

Ultraviolet Absorption Spectra

The apparatus used was a Beckman spectrophotometer, Model DU. The results are plotted as log E_m against the wave lengths in Angstrom units (2). The solvents employed were ethanol (95%) and a solution of sodium hydroxide (0.01*N*) in ethanol (95%).

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THE PREPARATION OF SODIUM CARBOXYMETHYLCELLULOSE¹

BY R. R. McLAUGHLIN AND J. H. E. HERBST

Abstract

The preparation of sodium carboxymethylcellulose from cellulose, sodium hydroxide, and sodium chloroacetate in the presence of water was investigated. The effects of temperature, excess of sodium hydroxide, ratio of water to cellulose, time of mixing, and manner of addition of the reagents were studied. The highest degree of substitution attained was 2.8.

Introduction

Sodium carboxymethylcellulose, the reaction product of cellulose, sodium chloroacetate, and sodium hydroxide, has become a material of industrial interest. Its preparation was first studied systematically by Chowdhury (1), who claimed to have prepared triply substituted sodium carboxymethylcellulose. Sakurada (3) subsequently repeated some of Chowdhury's work, but was unable to obtain a highly substituted product. The patent literature contains numerous references to carboxymethylcellulose of low degree of substitution.

Investigation by the authors (2) of the analytical methods used by Chowdhury showed that they are inapplicable to carboxymethylcellulose of high degree of substitution. The development of suitable methods and the introduction of the mechanical shredder for reactions of this kind made it of interest to re-investigate this field. This paper presents data on the effect of the reaction conditions on the degree of substitution, with particular emphasis on products of high degree of substitution.

Experimental

The general method used in the preparation of sodium carboxymethylcellulose was as follows. Approximately 100 gm. of cellulose (or an equivalent quantity of partially substituted sodium carboxymethylcellulose) and water were placed in a Baker Perkins Inc. size 4-AN2 stainless steel laboratory shredder and shredded for 30 min. Reagent grade flake sodium hydroxide was then added, and, after 10 min., sodium chloroacetate. Shredding was continued for the desired time, during which the temperature was maintained at 10°C. The mixture was then removed from the shredder and stored at the desired reaction temperature until the sodium chloroacetate had fully reacted; this generally required 12 hr. at 45°C., two days at 25°C., two weeks at 10°C., and several months at 0°C. Thus under the conditions used most of the reaction took place after removal of the mass from the shredder. Because the reaction is strongly exothermic, care was taken to prevent the temperature in the center of the mass from rising above that of the surroundings.

¹ Manuscript received June 20, 1950.

Contribution from the Department of Chemical Engineering, University of Toronto, Toronto, Canada. From a thesis submitted by J. H. E. Herbst in partial fulfillment of the requirements for the Ph.D. degree in the University of Toronto.

The disappearance of sodium chloroacetate was determined in the following way. A small sample (0.1 gm.) of the reaction mixture was dissolved in 1 ml. of water and an excess of an aqueous cupric nitrate solution was added to precipitate cupric carboxymethylcellulose and cupric hydroxide. The mixture was filtered, and an excess of silver nitrate solution was added to the filtrate. After removal of the precipitated silver chloride by filtration the solution was made strongly alkaline (25% sodium hydroxide) by the addition of solid sodium hydroxide, and kept at 110°C. for 30 min. The mixture was then cooled and carefully acidified with concentrated nitric acid. A residue of silver chloride indicated sodium chloroacetate.

Because the neutralization of chloroacetic acid by sodium hydroxide evolves considerable heat, sodium chloroacetate was not prepared *in situ* but separately as follows. A cold solution of 250 gm. of sodium hydroxide in 2 liters of absolute ethanol was added, with stirring and cooling, to 500 gm. of chloroacetic acid, until the mixture was just alkaline to phenolphthalein. The precipitated sodium chloroacetate was filtered off by suction, freed from as much solution as possible by the use of a rubber dam, and allowed to dry in the air; the yield was 85-90%.

Several experiments were also carried out in which sheet pulp was steeped in aqueous sodium hydroxide solution and pressed, as is the practice in the manufacture of viscose. The mixture was then further reacted with sodium chloroacetate. Since the degrees of substitution from both methods were similar under otherwise similar conditions, and since the first method permitted a much wider latitude of conditions, no further work was done with the latter procedure.

The cellulose used was Tenacell, a sulphite pulp of high alpha-cellulose content in sheet form, obtained from Riordon Sales Corporation. Its content of nonvolatile material was 95% and its ash negligible. Most determinations of the degree of substitution were carried out by the copper method described in (2).

Part I: Preparations 1-17

Part I comprises a number of preparations in which the molecular ratio of sodium chloroacetate to anhydroglucose units was constant (1.25: 1) and the effects of temperature, ratio of sodium hydroxide to sodium chloroacetate, ratio of water to cellulose, and shredding time were investigated. The experimental conditions and the degree of substitution obtained in 17 preparations of sodium carboxymethylcellulose are given in Table I.

A comparison of preparations 3, 4, and 5, or 12, 13, 14, and 15 shows that a decrease in temperature resulted in a small increase in efficiency. Preparations 8, 16, and 17 show that excess sodium hydroxide decreased efficiency. A comparison of preparations 4, 6, 7, 8, and 9 shows that under the conditions used the optimum ratio of water to cellulose was approximately 1.3: 1; this

TABLE I
REACTION CONDITIONS AND RESULTS OF PREPARATIONS 1-17

No.	Mole ratio NaOH CICH ₂ COONa	Ratio water cellulose*	Shredding time, hr.	Reaction temp., °C.	Reaction efficiency†, %	Degree of substitution	Water solubility‡
1	1.02	0.40	1	10	25	0.31	P
2	1.02	0.40	3	10	64	0.80	P
3	1.02	0.40	6	10	67	0.84	P
4	1.02	0.40	6	25	63	0.79	P
5	1.02	0.40	6	45	62	0.77	P
6	1.02	0.75	6	25	66	0.83	P
7	1.02	1.30	6	25	69	0.86	
8	1.02	1.50	6	25	64	0.80	
9	1.02	3.00	6	25	31	0.39	F
10	1.26	1.70	1	10	62	0.78	
11	1.26	1.70	3	10	61	0.76	
12	1.26	1.70	6	0	62	0.77	
13	1.26	1.70	6	10	60	0.75	
14	1.26	1.70	6	25	56	0.70	
15	1.26	1.70	6	45	50	0.63	
16	1.40	1.50	6	25	56	0.70	
17	2.00	1.50	6	25	45	0.56	P

*Based on air-dry weight.

†The number of sodium carboxymethyl groups substituted for 100 molecules of sodium chloroacetate added.

‡P—presence of unreacted particles.

F—presence of fibers.

coincided with the region of greatest solubility. Increasing the shredding time increased the efficiency, but only when the water-cellulose ratio was small, as shown by preparations 1, 2, and 3, and 10, 11, and 13.

Part II: Preparations 18-25

Part II consists of a number of preparations in which the ratio of sodium chloroacetate to cellulose was higher than that in Part I, and in which the influence of the ratio of water to cellulose and of the manner of addition of the reagents at the higher levels of substitution was observed. Preparations 18, 19, 23, 24, and 25 were multiple-stage preparations involving repeated additions of sodium hydroxide and sodium chloroacetate. The reaction was allowed to go to completion before each further addition, and no purification was effected between stages. The reactions were carried out at 25°C., after the reaction mixture had been shredded for two hours at 10°C. The amounts of reagents added were corrected to allow for the removal of samples. Preparations 20, 21, and 22 consisted of single large additions of sodium chloroacetate and sodium hydroxide; the general procedure was similar to that used for the preparations in Part I; the reaction temperature was 25°C. and the shredding time six hours.

Preparation 18

Preparation 6, in which the water-cellulose ratio was 0.75:1, served as the first stage in this series. Each successive stage consisted of the addition of

1.02 moles of sodium hydroxide per mole of sodium chloroacetate and 1.25 moles of sodium chloroacetate per mole of anhydroglucose unit. All samples contained insoluble unreacted particles.

Preparation 19

Preparation 7, in which the water-cellulose ratio was 1.30: 1, served as the first stage in this series. Further treatment was as in preparation 18. All samples contained insoluble unreacted particles.

Preparations 20-22

In preparations 20, 21, and 22 the molecular ratio of sodium hydroxide to sodium chloroacetate was 1.02: 1 and that of sodium chloroacetate to anhydroglucose units 2.5: 1, 5: 1, and 10: 1, respectively. The water-cellulose ratio was 1.30: 1. All samples contained insoluble unreacted particles.

Preparation 23

Whereas in all other preparations the reaction mixture was a powder, in this preparation enough water was added at various stages to produce and maintain a puttylike consistency after the third stage. Otherwise, the preparation was similar to preparation 19. Because mixing of this mass in the shredder produced very much heat, the time of mixing was 10 min., rather than two hours, as usual. Table II gives the water-cellulose ratio at each stage; water produced by the reaction was neglected in the calculation.

TABLE II
WATER-CELLULOSE RATIO IN PREPARATION 23

Stage	Ratio water cellulose*	Stage	Ratio water cellulose
1	1.42	9	2.90
2	1.42	10	3.45
3	2.00	11	3.88
4	2.90	12	3.88
5	2.90	13	4.60
6	2.90	14	5.35
7	2.90	15	5.35
8	2.90		

*Dry basis; sodium carboxymethylcellulose calculated as cellulose.

Preparation 24

Preparation 8, in which the water-cellulose ratio was 1.50: 1, served as the first stage in this series. Further treatment was as in preparation 18. After the third stage this material was discarded because it became puttylike and hot.

Preparation 25

In this series each stage consisted of the addition of 1.02 moles of sodium hydroxide per mole of sodium chloroacetate and 2.5 moles of sodium chloroacetate per mole of anhydroglucose unit. The ratio of water to cellulose was 1.50: 1. All samples contained insoluble unreacted particles.

The results of the experiments described above are given in Table III. It is seen that for efficient reaction more water was required as the degree of substitution increased (preparations 18, 19, 23, and 24) and that a given quantity of reagents was utilized more efficiently when it was allowed to react in small portions, rather than all at once (preparations 19, 20, 21 and 22, or 24 and 25). The highest degree of substitution reached was 2.8 (preparation 23).

TABLE III
RESULTS OF PREPARATIONS 18-25

Mole ratio $\text{CICH}_2\text{COONa}$ anhydroglucose (cumulative)	Efficiency* by stage(s)					Overall efficiency					Degree of substitution						
	18	19	23	24	25	18	19	20- 22	23	24	25	18	19	20- 22	23	24	25
1.25	66	65	69	64		66	65		69	64		0.83	0.81		0.86	0.80	
2.5	44	57	47	53	55	55	61	48	58	58	55	1.38	1.53	1.20	1.45	1.46	1.37
3.75	—	26	18	30		—	50		45	49		—	1.86		1.68	1.84	
5	18	20	34		15	37	42	33	42		35	1.83	2.11	1.63	2.11		1.75
6.25	—	—	10			—	—		36			—	—		2.24		
7.5	9	6	5		5	27	30		31		25	2.05	2.26		2.30		1.88
8.75	—	16				—		29				—		2.50			
10		4	—			24	17	—				2.37	1.67	—			
11.25	—	11				—		25				—		2.77			
12.5		2				19		—				2.41		—			
13.75								20						2.74			
15								—						—			
16.25								17						2.80			
17.5								—						—			
18.75								15						2.82			

NOTE:—A dash indicates that the sample concerned was prepared but not analyzed.

* The number of sodium carboxymethyl groups substituted for 100 molecules of sodium chloroacetate added.

Part III: Repetition of Chowdhury's Work

Part III (preparation 26) represents a repetition of Chowdhury's work (1) on highly substituted carboxymethylcellulose, in which a much higher water-cellulose ratio and no mechanical agitation were used.

The reaction conditions and results obtained are shown in Table IV. Chowdhury did not specify the size of the sample removed at each stage, except at stage 4 where approximately half the reaction mixture was removed;

reasonable estimates of sample sizes are given in Table IV. The degrees of substitution were determined by the copper method described in (2). After stages 1 and 2 the material contained insoluble fibers.

TABLE IV
REACTION CONDITIONS AND RESULTS OF PREPARATION 26

Stage	Cellulose*† present, gm.	Total weight, gm.†	Ratio water cellulose*‡	Mole ratio ClCH_2COOH Anhydroglucose (cumulative)	Weight of sample, gm.	Efficiency, %		Degree of substitution
						For over- stage	Over- all	
1	5.00	83	6.5	9.3	14	7.0	7.0	0.65
2	4.14	149	14.4	20.5	18	5.9	6.4	1.31
3	3.64	213	23.4	33.2	23	3.4	5.2	1.74
4	3.24	273	33.5	47.5	145	2.8	4.5	2.14
5	1.52	209	54.8	77.9	19	0.5	3.0	2.30
6	1.38	—	78.3	111	—	0.4	2.2	2.43

*Sodium carboxymethylcellulose, calculated as cellulose.

†Before removal of sample.

‡Water produced by the reaction neglected in the calculation.

The results suggest that Chowdhury did not obtain a triply substituted carboxymethylcellulose; it appears likely that he was misled by faulty analytical methods. A comparison of all of Chowdhury's data with those presented here indicates that the use of the shredder gives higher degrees of substitution and higher reaction efficiencies than those obtained by Chowdhury.

Acknowledgments

The authors wish to thank Dr. A. G. Nickle for advice and assistance, the Ontario Research Foundation for the use of the shredder, and the School of Engineering Research, University of Toronto, for financial aid.

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THE DETERMINATION OF THE DEGREE OF SUBSTITUTION OF CARBOXYMETHYLCELLULOSE OVER THE ENTIRE SUBSTITUTION RANGE¹

BY R. R. McLAUGHLIN AND J. H. E. HERBST

Abstract

The published methods for the determination of the degree of substitution of carboxymethylcellulose were found to be unsatisfactory for samples of high degree of substitution. Two methods were developed: one comprises the removal of the impurities from crude sodium carboxymethylcellulose by dialysis or washing with ethanol and determination of the sodium content; the other is based on the precipitation of cupric carboxymethylcellulose under controlled conditions, purification, and determination of the copper content.

Introduction

In the study of highly substituted sodium carboxymethylcellulose (5) it was necessary to have a satisfactory method for the determination of the degree of substitution in that range. The literature contains references to various methods for the determination of the degree of substitution of carboxymethylcellulose in the substitution range 0 to 1.5. These involve the preparation of the sodium salt and determination of the sodium content (3, 6, 7, 8); the preparation of the free acid and its titration (1, 3, 6, 7, 8); the precipitation of a nonalkali metal salt, especially copper, and determination of the metal content (6, 7); or the splitting of the ether linkages and determination of the glycollic acid formed (3). In one paper (2) the first and third methods mentioned above were used over the entire substitution range.

In this study the free acid was found to be unsatisfactory owing to its uncertain solubility characteristics at high degree of substitution. The methods based on the sodium and cupric salts were investigated and found to be applicable in the high substitution range only after considerable modification. After this work had been finished an analytical procedure (9) based on the cupric salt was published embodying some of the principles discussed below.

The sodium carboxymethylcellulose prepared as described in an accompanying paper (5) contained the following impurities: water, sodium chloride, sodium glycolate, sodium carbonate, and sodium hydroxide.

Experimental

The Sodium Salt Method

The methods based on the sodium salt consist of the removal of the impurities from crude sodium carboxymethylcellulose by dialysis or washing with ethanol and determination of the sodium content.

¹ Manuscript received June 19, 1950.

Contribution from the Department of Chemical Engineering, University of Toronto, Toronto, Canada. From a thesis submitted by J. H. E. Herbst in partial fulfillment of the requirements for the Ph.D. degree in the University of Toronto.

(1) Dialysis

A piece of cellophane dialysis tubing (3 cm. diam., 20 cm. long), tied at one end, is washed in running water for eight hours. Preliminary experiments with various dialysis membranes had shown that low results for the degree of substitution are obtained when this treatment is omitted, probably because the cellophane contains an additive which on dialysis is transferred to the "purified" sodium carboxymethylcellulose. A sample of the crude sodium carboxymethylcellulose containing 0.1 to 0.5 gm. of sodium carboxymethylcellulose is placed in the tube, moistened with a little water (if a sample containing much insoluble matter is used it is advisable to disperse it in a Waring Blender), and dialyzed with distilled water which is renewed at the rate of 400 ml. per hr., the liquid hold-up in the dialyzing vessel (not including the volume of the solution undergoing dialysis) being 10 to 25 ml. Tap water was not used for dialysis because it was thought likely that ion exchange would take place. During dialysis a considerable amount of osmosis takes place.

Purification is considered complete when sodium bicarbonate, which is occasionally found at this stage or at a corresponding stage in the purification by ethanol, described below, sodium chloride, sodium hydroxide, and sodium carbonate are absent. This usually occurs after 20 hr. of dialysis.

A sample of the mixture must be acid to phenolphthalein and show no turbidity when nitric acid and silver nitrate solution are added. Since sodium carboxymethylcellulose, especially in the higher ranges of substitution, is acid to phenolphthalein at room temperature but often alkaline to it at the boiling point, the following test for sodium bicarbonate is used. The aqueous solution or suspension, with added phenolphthalein, is boiled in a test tube for three minutes; it usually becomes red. The test tube is stoppered and cooled; a red color indicates bicarbonate.

No direct test for sodium glycollate was made (the color test described by Feigl (4) is not applicable in the presence of sodium carboxymethylcellulose (3)), but the fact that the sodium content remained constant on continued dialysis showed that sodium glycollate was absent when the tests for the other impurities were negative.

After dialysis the pH* of the mixture, generally between 6.5 and 7.3, which is below the values (8.0-8.1) reported in the literature (1, 6), is adjusted by potentiometric titration with a 0.1% aqueous solution of sodium hydroxide. The end point falls between pH 7.3 and 8.8, and is generally higher for sodium carboxymethylcellulose of higher degree of substitution. The resulting increase in sodium content of the sodium carboxymethylcellulose is always less than 2%, based on sodium.

Duplicate samples of the purified mixture are placed in platinum crucibles, evaporated to dryness at 100°C., and dried to constant weight at 125°C. in

*The pH values reported were determined with a Beckman model G instrument with glass electrode.

vacuo; the vacuum drying period usually requires 18 hr. The dry sodium carboxymethylcellulose is weighed,* an excess of concentrated hydrochloric acid (usually 0.5 ml.) added, the mixture evaporated at 110°C., ignited at 600°C., and the resulting sodium chloride weighed (10).

The degree of substitution is then calculated from the formula

$$\text{Degree of substitution} = \frac{2.774 r}{1 - 1.369 r},$$

where r is the mean ratio of sodium chloride to sodium carboxymethylcellulose.

If it is desired to determine the sodium carboxymethylcellulose content of crude sodium carboxymethylcellulose, the initial sample is weighed, the losses incurred during testing and transfer of the mixture are determined, and the sodium carboxymethylcellulose content is calculated from the weight of the dry pure sodium carboxymethylcellulose. It was found that the recovery of sodium carboxymethylcellulose from crude sodium carboxymethylcelluloses of known composition ranged between 97 and 101%.

(2) Purification by Ethanol

Preliminary experiments on the removal of the impurities from crude sodium carboxymethylcellulose by washing with a mixture of ethanol and water disclosed the following facts.

- (a) The solubility of sodium carboxymethylcellulose in aqueous ethanol increases with increasing degree of substitution and increasing water-ethanol ratio. It is desirable to use 95% ethanol with most samples.
- (b) The solubility of sodium carbonate in 95% ethanol is extremely small.

Consequently the following procedure was designed, which was found satisfactory over a limited range of degree of substitution (see "Results and Conclusions"). A sample of crude sodium carboxymethylcellulose containing 0.1 to 0.5 gm. of sodium carboxymethylcellulose is dissolved in 30 ml. of water or dispersed in the Waring Blender if necessary. Concentrated hydrochloric acid is added until the boiling solution becomes acid to phenolphthalein. It is then made just alkaline with sodium hydroxide. The hot mixture is poured dropwise into enough agitated absolute ethanol to make the final composition 95% ethanol. The resulting precipitate is dispersed in a Waring Blender if large particles are present, and washed by decantation with 95% ethanol, until a small sample shows no impurities when tested according to the methods described in Section 1. The mixture is filtered and the solid dissolved in 10 to 50 ml. of water. The pH of the solution thus obtained is in the same range as that of the solutions from dialysis. From this point the method is identical with the dialysis method.

The Cupric Salt Method

Examination of the work done on the cupric carboxymethylcellulose method by earlier investigators showed that the copper content of the precipitate

*All gravimetric work was carried out with platinum crucibles contained in glass weighing bottles, owing to the hygroscopicity of most of the solids weighed.

increases with increasing pH of the solution from which precipitation takes place. It was thought that this was due to cupric hydroxide when the pH was too high and to free carboxyl groups when it was too low, and that the feasibility of the method depended on the existence of a pH range in which fully neutralized cupric carboxymethylcellulose only could be precipitated.

The existence of such a range was demonstrated by a series of potentiometric titrations. Typical examples are given in Figs. 1 and 2. Fig. 1 represents the titration of a solution of 1 gm. of cupric nitrate trihydrate in 1 liter of water, to which hydrochloric acid had been added, with a 0.8 N solution of sodium hydroxide. The curve indicates that cupric hydroxide is precipitated at pH 6 to 7; other similar titrations and titrations of suspensions of cupric hydroxide with acid occasionally gave somewhat different results, probably owing to the fact that the reaction is slow; in no case was a precipitate of cupric hydroxide found to coexist with a solution of pH 5 or lower. Examples *a*, *b*, and *c* (Fig. 2) represent similar titrations of acidified solutions of sodium carboxymethylcellulose in 1 liter of water to which had been added 3 gm. of cupric nitrate trihydrate. In "*a*" crude sodium carboxymethylcellulose of degree of substitution 2.82, in "*b*" purified sodium carboxymethylcellulose of degree of substitution 2.82, and in "*c*" purified sodium carboxymethylcellulose of degree of substitution 0.75 were used.

It was concluded from these curves that when cupric carboxymethylcellulose is precipitated in the pH range 4.2 to 4.5, it will be fully neutralized by copper and uncontaminated by cupric hydroxide. The result is independent of the degree of substitution; the impurities contained in crude sodium carboxymethylcellulose do not interfere.

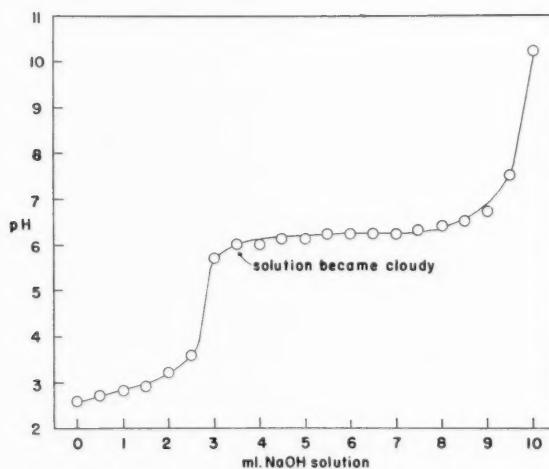


FIG. 1. Titration of an acidified solution of cupric nitrate with sodium hydroxide.

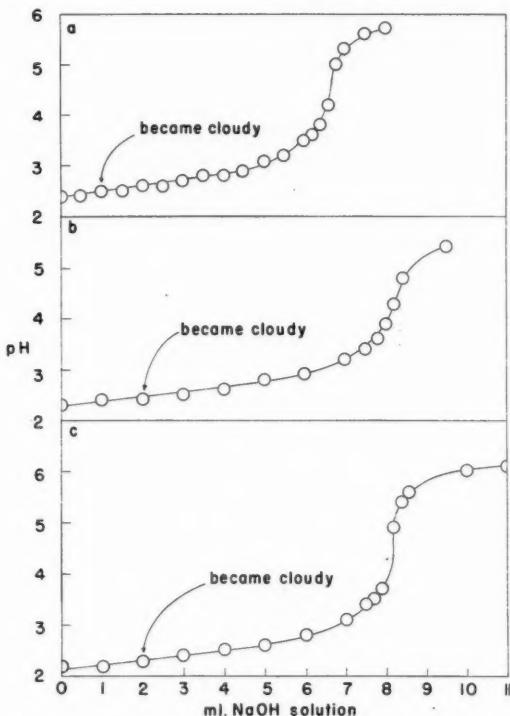


FIG. 2. Titration of acidified solutions of cupric nitrate and carboxymethylcellulose with sodium hydroxide.

In the purification of cupric carboxymethylcellulose precipitated in this manner there is a possibility that the cupric nitrate dissolved in the solution associated with the precipitate after filtration might give rise to a precipitate on the addition of wash water. If this effect is to be negligibly small the concentration of cupric nitrate must be small. It was found, however, that the presence of the impurities in crude sodium carboxymethylcellulose prevents the precipitation of cupric carboxymethylcellulose at low cupric nitrate concentrations. Therefore the following procedure, involving a preliminary purification, was developed.

A sample of crude sodium carboxymethylcellulose containing between 0.1 and 0.5 gm. of sodium carboxymethylcellulose is added to 1 liter of water (any lumps present are dispersed with a Waring Blender) and the mixture made slightly alkaline, if necessary. Thirty milliliters of 10% aqueous solution of cupric nitrate trihydrate is added with stirring; if, owing to the inhibition mentioned above, no precipitation takes place, more cupric nitrate solution is added. The resulting precipitate of cupric carboxymethylcellulose, containing a little cupric hydroxide, is filtered and dispersed in 200 ml. of

water in a Waring Blender; 800 ml. of water and 10 ml. of cupric nitrate solution are added, and the mixture is acidified to pH 2.5 with concentrated hydrochloric acid and titrated potentiometrically to pH 4.2 to 4.5 with a 0.8 N solution of sodium hydroxide. The precipitate is filtered off and sucked as dry as possible on a coarse sintered glass funnel. A weight of less than 1 gm. is thus attained. Although the precipitate is often sufficiently pure for copper analysis at this stage, it may be disintegrated in a Waring Blender with a little 95% ethanol (to facilitate filtration), filtered and washed with water until the washings are free of copper, by potassium ferrocyanide, and of chloride, by silver nitrate.

Duplicate samples of the precipitate are placed in platinum crucibles and dried to constant weight at 125°C. *in vacuo*; overnight drying was found to be satisfactory. The samples are weighed and ignited to constant weight. The degree of substitution is calculated from the formula

$$\text{Degree of substitution} = \frac{4.075 r}{1 - 2.232 r},$$

where r is the mean ratio of cupric oxide to cupric carboxymethylcellulose.

Results and Conclusions

Table I illustrates the reproducibility of the dialysis method; Table II that of the ethanol wash method; Table III that of the copper method; Table IV presents a comparison among the methods. All pertinent results are given.

TABLE I
THE DIALYSIS METHOD

Preparation*	Degree of substitution
4	0.77, 0.80
19- 1	0.86, 0.86
19-10	2.40, 2.41
23-15	2.70, 2.73, 2.74, 2.76

*In all tables, preparation numbers refer to those given in (5); in a double number the first is the preparation number, the second the stage number.

TABLE II
THE ETHANOL METHOD

Preparation	Degree of substitution
13	0.73, 0.75
23- 3	1.80, 1.83

TABLE III
THE COPPER METHOD

Preparation	Degree of substitution
13	0.71, 0.78
11	0.75, 0.76, 0.76
10	0.75, 0.79, 0.80
6	0.79, 0.86
3	0.83, 0.85
19-3	1.84, 1.86
25-3	1.86, 1.89
26-4	2.11, 2.20
26-6	2.41, 2.48
23-15	2.80, 2.80, 2.85, 2.90

TABLE IV
COMPARISON OF THE METHODS

Preparation	Degree of substitution*		
	Dialysis method	Ethanol method	Copper method
15	0.66		0.63
14	0.73		0.70
13	0.74	0.74	0.75
12	0.76		0.77
11	0.76		0.76
10	0.79		0.78
8	0.84		0.80
2	0.84		0.80
6	0.85		0.83
3	0.85		0.84
23-3	1.78	1.81	1.68
19-10	2.40		2.41
23-9	2.68		2.77
23-15	2.73		2.82

*Calculated from the mean of all "r" values obtained.

It is seen that the dialysis method is satisfactory over the entire substitution range; the ethanol wash method is inapplicable to carboxymethylcellulose of degree of substitution higher than 2, where results which are nonreproducible and high, as compared with the other methods, are obtained; the copper method is best suited for carboxymethylcelluloses of high degree of substitution, as filtration of the precipitate becomes faster as the degree of substitution increases.

Tables I to IV indicate satisfactory reproducibility and agreement among the methods within their range of applicability; the results rarely differ by more than 0.1 unit of substitution. The data obtained in this study and in (5) indicate that the only previously published method (2) intended to cover the entire substitution range is unsatisfactory.

Acknowledgment

The authors wish to thank Dr. A. G. Nickle for advice and assistance, and the School of Engineering Research, University of Toronto, for financial aid.

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SYNTHESIS IN THE SERIES OF ERYTHRINA ALKALOIDS

II. STERIC CONFIGURATION OF THE SYNTHETIC BASE¹

BY E. D. CLAIR, F. H. Clarke, W. A. EDMISTON, AND K. WIESNER

Abstract

2-Cyclohexanone acetic acid ethyl ester oxime was hydrogenated in acidic medium to the corresponding amino ester, which is of the *cis* form, as by ring closure it gives a hexahydrooxindole which in turn is reduced by lithium aluminum hydride to *cis*-octahydroindole. Also, it has been shown that the amino ester can be transformed into *cis*-aminoethylcyclohexane. The high pressure Raney nickel hydrogenation of the oxime ester followed by lithium aluminum hydride reduction gave also *cis*-octahydroindole, although in neutral medium the *trans* form could have been expected.

In a previous communication (3) we described the synthesis of compound I, which we prepared for comparison with a degradation product of the *Erythrina* alkaloids. In this communication we shall describe the proof of the steric configuration of our synthetic base which is of the *cis* configuration with respect to the two carbons marked with asterisks. The starting material for our synthesis was 2-aminocyclohexyl acetic acid ethyl ester, II, obtained by hydrogenation of the oxime ester, III, in glacial acetic acid. It could be expected that by hydrogenation in acidic solution the *cis* isomer would be obtained, but, as this rule is by no means without exception, we felt that, especially in this case, the configuration proof is indicated. By refluxing II in alcohol, a ring closure to hexahydrooxindole, IV, takes place. Now, this reaction was much slower than we expected. After five days of refluxing 20% of the original amino ester was recovered unchanged. This led us to suspect that the reason for the slowness of the cyclization might be the *trans*-configuration of the amino ester. We therefore reduced IV with lithium aluminum hydride and obtained a base in all respects identical with *cis*-octahydroindole, V (1). We have obtained the same *cis*-hexahydrooxindole, IV, also by hydrogenation of oxindole with platinum oxide in glacial acetic acid at room temperature and atmospheric pressure. To corroborate the *cis*-configuration of the amino ester we reduced it to 2-aminocyclohexylethyl alcohol, VI, with lithium aluminum hydride, and this compound we converted into 2-aminoethylcyclohexane, VII, by treatment with hydroiodic acid and red phosphorus. This compound has been previously described in both the *cis*- and *trans*- forms (1). The melting point of the benzene sulphonamide of our compound was 161–162°C., which is identical with the melting point reported for the *cis*- and 30° higher than the melting point of the *trans*-compound. As it has now been proved that the amino ester obtained from the oxime, III, in acidic solution is *cis*-, we hoped that by high pressure and high temperature hydrogenation of III with Raney nickel in ether and subsequent lithium aluminum hydride reduction we would be able to prepare the as yet unknown

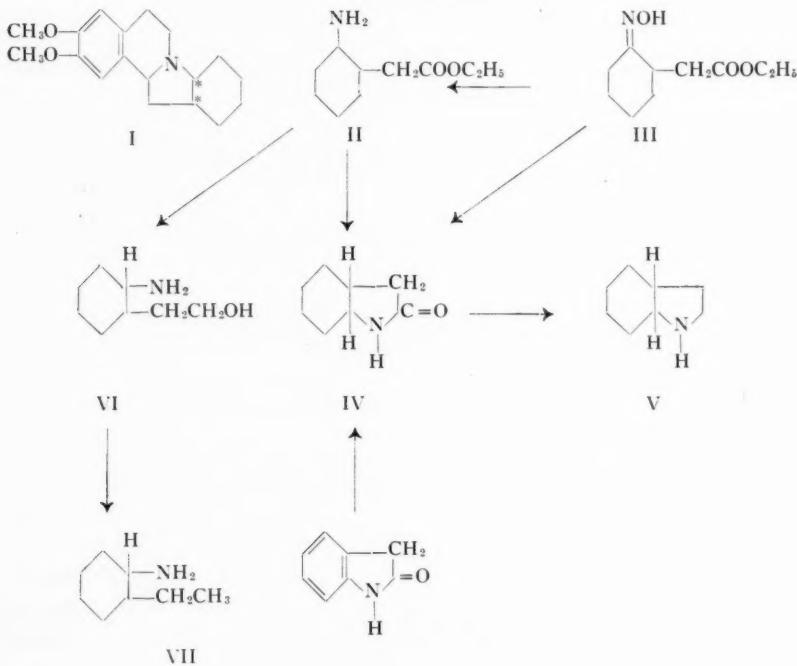
¹ Manuscript received July 25, 1950.

Contribution from the Department of Chemistry, University of New Brunswick, Fredericton, New Brunswick.

trans-octahydroindole. The hydrogenation product, however, after the lithium aluminum hydride reduction, gave an octahydroindole which proved identical with the *cis*-compound. Also no indication was found of the presence of a second isomer in the mother liquors.

As it seems that the *cis*-octahydroindole system is formed preferentially under very different conditions (see reference (1) for a discussion of this question) it seems likely that also in the natural substance derived from the *Erythrina* alkaloids the corresponding configuration is *cis*- and that therefore if structure I for the natural product is correct it will prove to be identical with one of the two *cis*-isomers.

FORMULA SCHEME



Experimental Part

2-Cyclohexanoneacetic Acid.—The 2-cyclohexanoneacetic acid needed for this work was prepared from ethylcyclohexanone-2-carboxylate and proved to be identical with the sample previously prepared according to the directions of Newman and Van der Werf (2). Cyclohexanone-2-carboxylate (142 gm.) was heated with 21 gm. of powdered sodium in 900 cc. of refluxing benzene for three hours. Ethylbromoacetate (129 gm.) was added and the refluxing con-

tinued for eight hours. The benzene was then washed, dried, and distilled off, and the residue hydrolyzed by refluxing with 800 cc. of 20% hydrochloric acid for 24 hr. Ether extraction of the diluted solution gave the crude acid, which was distilled in vacuum. The boiling point was 150–163°C. (10 mm.). The yield was 72 gm. The product crystallized on standing. The semicarbazone melted at 189–190°C. Calc. for $C_9H_{15}O_3N_3$: C, 50.69; H, 7.09; N, 19.71%. Found: C, 50.64; H, 7.01; N, 19.49%.

2-Aminocyclohexylacetic acid ethyl ester was prepared according to the procedure described in our previous communication (3). It was characterized as the crystalline picrolonate. It melted at 163–166°C. Calc. for $C_{20}H_{27}O_7N_5$: C, 53.45; H, 6.01; N, 15.59; OC_2H_5 , 10.22%. Found: C, 52.79; H, 5.89; N, 15.18; OC_2H_5 , 10.62%.

Hexahydroöxindole.—The crude amino ester (7.3 gm.) was refluxed in 150 ml. of absolute alcohol for 88 hr. After removal of the alcohol the residual oil was distilled in vacuum from a Hickmann flask. Two fractions were obtained, the unchanged amino ester (1.14 gm.), b.p. 132°C. (13 mm.), and hexahydroöxindole (4.73 gm.), a viscous colorless oil, b.p. 144–145°C. (5 mm.). The hexahydroöxindole was dissolved in ether, shaken with 0.2 M hydrochloric acid and sodium carbonate, and redistilled in vacuum from a collar flask for analysis. Calc. for $C_8H_{13}ON$: C, 69.03; H, 9.43; N, 10.06%. Found: C, 69.18; H, 9.39; N, 10.06%.

Reduction of Hexahydroöxindole with Lithium Aluminum Hydride

Hexahydroöxindole (1.57 gm.) was dissolved in ether and added to 2 gm. of lithium aluminum hydride dissolved in 500 ml. of absolute ether.

It was refluxed for seven hours and then water was added to decompose the excess of the reagent. After this, 50 ml. of 20% sodium hydroxide was added and the ether layer separated. The aqueous layer was extracted with ether and the combined extracts dried and evaporated.

The residual oil was dissolved in 45 ml. of dilute hydrochloric acid, the acidic solution extracted with ether, made basic, and octahydroindole extracted with ether. The yield was 0.98 gm. of oil which distilled at 11–12 mm., 70–80°C. (outside temperature) in a collar flask. The picrolonate melted after four recrystallizations from methanol at 227–230°C. and did not show any depression with an authentic specimen of *cis*-octahydroindole picrolonate. Calc. for $C_{18}H_{23}O_5N_5$: C, 55.52; H, 5.95; N, 17.99%. Found: C, 55.59; H, 5.95; N, 17.92%.

The picrate melted after four crystallizations from methanol at 141.5–143°C. It did not depress the melting point of authentic *cis*-octahydroindole picrate. Calc. for $C_{14}H_{18}O_7N_4$: C, 47.45; H, 5.12; N, 15.81%. Found: C, 47.48; H, 5.18; N, 15.74%.

2-Aminocyclohexylethanol VI

The crude amino ester (4 gm.) II was reduced by lithium aluminum hydride and worked up in the manner already described. The product was separated by fractional distillation from a small amount of octahydroindole and it distilled at 107–112°C. at 3 mm. The yield was 2.65 gm. A picrolonate melted after four crystallizations from methanol at 192.5–194°C. Calc. for $C_{18}H_{25}O_6N_5$: C, 53.20; H, 5.91; N, 17.24%. Found: C, 52.89; H, 6.09; N, 17.25%.

cis-Aminoethylcyclohexane, VII

2-Aminocyclohexylethanol (1.481 gm.) was refluxed with 90 cc. of hydroiodic acid and 9 gm. of red phosphorus for 12 hr. Then, 30 gm. of zinc was added and the whole refluxed for two more hours. The mixture was evaporated to dryness in vacuum, water was added, and the solution made alkaline. The thick suspension of zinc hydroxide was then extracted continuously for 48 hr. with ether. The ether was evaporated and the residue distilled in a collar flask in vacuum. It distilled at 10 mm. between 70–80°C. outside temperature. The yield was 0.411 gm. The benzene sulphonamide, prepared in the usual way, melted after six crystallizations from methanol at 161–162°C. Calc. for $C_{14}H_{21}O_2NS$: C, 62.88; H, 7.92; N, 5.24%. Found: C, 62.62; H, 7.95; N, 5.14%.

Hydrogenation of Oxindole

Oxindole (1 gm.) was hydrogenated in glacial acetic acid with 200 mgm. of platinum oxide. After 20 hr. the theoretical amount of hydrogen was taken up. The acetic acid was distilled off, and the product dissolved in ether and washed with a 5% sodium carbonate solution and water. The washings were repeatedly extracted with ether, as the product is water soluble. The yield of colorless oily product was quantitative. The product was distilled from a collar flask for analysis. It boiled at 150°C. (outside temperature; 6 mm.). Calc. for $C_8H_{13}ON$: C, 69.03; H, 9.41; N, 10.06%. Found: C, 68.97; H, 9.51; N, 9.85%.

Lithium aluminum hydride reduction of this compound in the manner already described gave *cis*-octahydroindole.

Raney Nickel Hydrogenation of 2-Cyclohexanoneacetic Acid Ester Oxime

The oxime ester III (5 gm.) was hydrogenated in 100 ml. of ether over a teaspoonful of Raney nickel. The temperature was 110°C. and pressure 2,200 lb. per sq. in. The uptake was completed overnight and the product was worked up as usual. The product (3.77 gm.) distilled at 128°–138°C. (outside temperature, 1 mm.) in a collar flask. It was reduced with lithium aluminum hydride in the manner already described. The octahydroindole obtained gave a picrolonate which melted at 229–231°C. A mixed melting point with *cis*-octahydroindole picrolonate showed no depression. Calc. for $C_{18}H_{23}O_5N_5$: C, 55.52; H, 5.95; N, 17.99%. Found: C, 55.67; H, 5.93; N, 18.00%.

Acknowledgments

This work has been performed on a grant from the National Research Council, Ottawa. We wish to thank the Rockefeller Foundation, New York, for a grant that enabled us to acquire the high pressure hydrogenation equipment. The analyses were performed by the Microanal. Laboratorium, Dr. R. Dietrich, in Zurich.

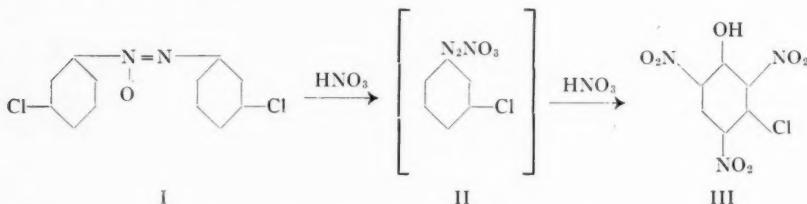
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NOTES

A Note on the Constitution of a Certain Nitration Product of 3,3'-Dichloroazoxybenzene

By refluxing 3, 3'-dichloroazoxybenzene (*I*) with concentrated nitric acid Bigelow and Steeves (2) obtained several nitration products. One of these compounds, designated *A*, with a melting point of 116°C. was thought to be 3, 3'-dichloro-5-nitroazoxybenzene. Unlike a typical azoxy compound, the reduction of *A* with tin and hydrochloric acid took place with difficulty forming mostly tarry materials.



The parachor of *A* was determined by Bigelow and Keirstead (1). On the basis of the structure suggested by Bigelow and Steeves, the parachor value (578.0) calculated from the constants agrees poorly with the value (480.5) calculated from the measurements. It was also noted that compound *A* was highly soluble in water to give a yellow solution. These facts suggested the presence of a hydroxyl group.

A re-examination of the physical and chemical properties of *A* shows that it is actually 3-chloro-2, 4, 6-trinitrophenol (III). Calc. for $C_6H_2N_3ClO_7$: C, 27.3; H, 0.88; N, 15.9; Cl, 13.46%. Found (original sample recrystallized from benzene, m.p. 114.5°C.*): C, 27.65; H, 1.009; N, 16.80; Cl, 14.65%. It was later found that a purer sample with a melting point of 116°C. could be obtained by crystallizing from dilute hydrochloric acid. The solution in water is strongly acid. A 0.02 molar solution has a pH of 2.0. Neutral equivalent: Calc. for $C_6H_2N_3ClO_7$: 263.5. Found, 262. On the basis of the structure, 3-chloro-2, 4, 6-trinitrophenol, parachor values are: calc. 435.6; found: 410.8.

Compound A is identical with 3-chloro-2, 4, 6-trinitrophenol prepared according to the method of Hodgson and Moore (3) in these respects: melting point and mixed melting point, 116°C.; ammonium salt, yellow, 223-224°C.; dimethylaniline salt, yellow, 189-190°C.; highly soluble in water to give a yellow solution which dyes wool a fast yellow; precipitates from dilute hydrochloric acid in colorless rectangular prisms.

* All melting points are uncorrected.

Considering the stable nature of azoxy compounds the appearance of 3-chloro-2, 4, 6-trinitrophenol as one of the chief nitration products is unexpected. However, we were not able, after many trials, to obtain the relatively high yield, 20%, reported by Bigelow and Steeves. Some runs gave practically no trace of a water soluble product.

The formation of 3-chloro-2, 4, 6-trinitrophenol appears to be related to the mechanism suggested by Schmidt (4) for the action of fuming nitric acid at room temperature on certain azo compounds. The products of the reaction were a diazonium (II) compound and a nitro compound. Since this procedure was found to give the same products when the corresponding azoxy compound was used, Schmidt proposed the following mechanism to account for the reaction: oxidation of the azo compound to an azoxy compound; fission, between the nitrogen atoms of the azo group and the second benzene ring, to form a diazonium compound. At the same time the second benzene ring was nitrated.

In a similar manner we may assume that the first action of the concentrated nitric acid (possibly containing brown fumes) used by Bigelow and Steeves was to form 3-chlorodiazonium nitrate (II). The latter compound was probably changed to 3-chlorophenol at or near refluxing temperature. Continued refluxing could then produce the nitrated product (III). In support of this mechanism we found evidence for the presence of a diazonium compound in the solution resulting from the treatment of 3, 3'-dichloroazoxybenzene with cold fuming nitric acid; the solution coupled with dimethylaniline and with phenol to produce a dye in each case. As further evidence that oxidation and decomposition took place in the nitration method of Bigelow and Steeves, we found that every nitration produced a powerful lachrymatory substance which came over in the steam distillate as a few drops of a colorless liquid insoluble in water. These properties correspond to those of tetranitromethane which is formed during the nitration of many organic compounds.

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RECEIVED AUGUST 3, 1950
CANADIAN ARMAMENT RESEARCH
AND DEVELOPMENT ESTABLISHMENT,
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AND
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Apparatus to Deliver Liquid at Constant Rate

An apparatus is described which delivers liquids at a constant predetermined rate and which is capable of operating overnight without attention. The apparatus was found useful in various washing operations and in dialysis, and was used without failure for 18 months.

Preliminary attempts to build an apparatus based on a constant level device and orifice were unsuccessful because small particles suspended in the liquid tended to plug the orifice. In the apparatus described, the liquid is filtered before it reaches the orifice.

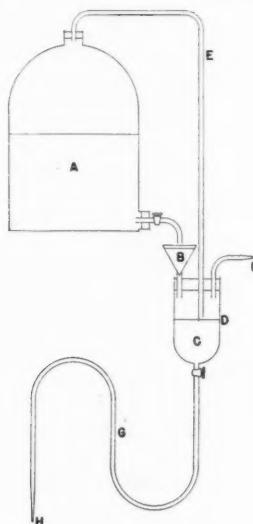


FIG. 1

The liquid is stored in the bottle *A*, from which it flows through the filter *B* into the reservoir *C*. A constant level is maintained at *D*: air is admitted to *A* through the rubber tube *E* whenever the level in *C* falls sufficiently. The orifice *F* admits the necessary air. The liquid passes through the tube *G*, made of rubber or other suitable material, and through the glass orifice *H*. The rate of flow is controlled by the vertical distance between *D* and *H* and the dimensions of *H*.

RECEIVED JUNE 20, 1950
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CANADIAN JOURNAL OF RESEARCH

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